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SIGNIFICANCE OF ANAEROBIC ORGANISMS IN PERITONITIS DUE TO LIVER AUTOLYSIS

A BACTERIOLOGIC STUDY OF THE PERITONEAL EXUDATES

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The medical literature of the past twenty years contains numerous reports designating the Welch bacillus as a factor in the etiology of various pathologic conditions, both clinical and experimental. The most recent are the reports of Andrews, Rewbridge and Hrdina, who contended that the Welch bacillus is the cause of death following the intraperitoneal introduction of various sterile preparations of liver and of bile salts. These investigators made their observations on dogs and concluded that the Welch bacillus is a normal inhabitant of dog tissue. In view of the fact that these observations resulted from experimental work on liver autolysis, a brief review of the literature is indicated.

Mann [1] in his studies on the effect of hepatectomy in the dog observed that if a small piece of the liver was allowed to remain in the peritoneal cavity the animal died much sooner than if the liver was entirely removed. Mason, Davidson, Matthew and Rastello,[2] thinking that there might be some relation between the death of the dogs and the toxic manifestations encountered after the intravenous administration of an anticoagulant from dog liver, studied the effect of placing small pieces of aseptically removed liver in the peritoneal cavity of dogs. Their conclusions were that this autolysis of the liver in vivo produces a powerful toxin which on absorption causes death in a few hours. Ellis and Dragstedt [3] studied the autolysis of dog liver in vivo and con-

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1. Mann, F. C.: Personal communication to the authors.

2. Mason, E. C.; Davidson, E. C.; Matthew, C. W., and Rastello, P. B.: A Study of Tissue Autolysis in Vivo, J. Lab. & Clin. Med. **10**:622 (May) 1925. Mason, E. C.; Davidson, E. C., and Rastello, P. B.: Study of Tissue Autolysis in Vivo: Pharmacological Study of Toxic Material, ibid. **10**:906 (Aug.) 1925. Mason, E. C.; Davidson, E. C., and Matthew, C. W.: Tissue Autolysis in Vivo; Observations Using Spleen, ibid. **10**:997 (Sept.) 1925.

3. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, Arch. Surg. **20**:8 (Jan.) 1930.

cluded that death of the dogs is due to bacterial peritonitis. They described the bacterium as being a large, gram-positive, gas-forming anaerobic bacillus which is normally present in the liver of the adult dog and is similar to, but not identical with, the Welch bacillus. Andrews and Hrdina,[4] believing that the dogs die too soon after the introduction of the liver substance for their death to be due to an ordinary infectious process, and observing large quantities of gas in the peritoneal cavity, concluded that the offending organism is the Welch bacillus and that the dogs die as the result of toxemia caused by the Welch bacillus. They further reported that this infection can be induced by the implantation of liver substance previously sterilized by autoclaving, and concluded that there resides in the implanted material some toxic substance which makes the infection by the Welch bacillus a practical certainty. They assumed that this organism is a normal inhabitant of dog tissue and invades the peritoneal cavity as a result of the devitalizing action of the toxic material. Rewbridge,[5] after studying peritonitis produced by bile and sterile bile salt solutions, reported that these substances likewise produce fatal peritonitis caused by the Welch bacillus. Andrews, Rewbridge and Hrdina,[6] in a further study, concluded that infection by the Welch bacillus can be initiated in the pelvis, in the chest or in muscular tissue by the injection of sterile bile salt solutions, bile or sterile liver extract.

We have been investigating this problem for the past three years. In certain fundamental respects our results are at complete variance with these sweeping conclusions. Our experiments cover several phases of the rather complex subject. A detailed account of our results will be found in the protocols and tables which follow.

GENERAL OBSERVATIONS

We do not find Clostridium Welchii to be a normal inhabitant of dog liver or dog muscle. Our experimental methods and the observations substantiating this statement were reported in detail in a previous publication.[7] In a series of normal dogs we were able to demonstrate in liver and muscle tissue gram-positive, gas-forming anaerobic organisms which on superficial study might be confused with the Welch bacillus. These organisms, however, were not identical with Cl. Welchii in

4. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. **52**:61 (Jan.) 1931.

5. Rewbridge, A. G.: The Etiologic Rôle of Gas-Forming Bacilli in Experimental Bile Peritonitis, Surg., Gynec. & Obst. **52**:205 (Feb.) 1931.

6. Andrews, S.; Rewbridge, A. G., and Hrdina, L.: Causations of Bacillus Welchii Infections in Dogs by the Injection of Sterile Liver Extracts or Bile Salts, Surg., Gynec. & Obst. **53**:176 (Aug.) 1931.

7. Trusler, H. M., and Reeves, J. R.: The Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, Arch. Surg. **28**:479 (March) 1934.

morphology or in cultural characteristics. What is more important, in no case could they be shown to produce an exotoxin in vitro. We have shown these organisms to constitute several strains of a vaguely classified group of anaerobic, spore-forming saprophytes characterized by their ability to form great quantities of gas during the rapid digestion of protein and to live at high temperature. They usually are gram-positive and in most instances form terminal spores. The conditions under which these organisms cause death in dogs will be discussed later in this paper.

When pieces of liver removed aseptically from one dog are introduced with the usual aseptic precautions into the peritoneal cavity of another dog, death results in a few hours. This is a common observation of many investigators, and a detailed account of this phase of our work is unnecessary. Our observations were made on a series of about thirty dogs, and in every instance we recovered from the peritoneal exudates large, gram-positive, gas-forming anaerobes. These bacteria were identical with the organisms normally found as the bacterial flora of the liver of the adult dog and of dog muscle. In no instance were we able to isolate Cl. Welchii or any organism that produced an exotoxin in vitro. In general our observations on this phase of the problem were in complete agreement with the results reported by Ellis and Dragstedt. We found, however, that the peritoneal exudate of these dogs contained not only the liver organism but other anaerobes normally found in dog muscle. This fact, together with the observation that staphylococci, streptococci and colon bacilli were also present, caused us to conclude that probably we were contaminating the pieces of liver while placing them in the peritoneal cavity or that possibly the bacteria normally present as the flora of the abdominal wall gained access to the peritoneal cavity through the peritoneal incision.

EXPERIMENTS WITH FRESH AUTOCLAVED LIVER

Ellis and Dragstedt reported that when chunks of fresh liver are sterilized by autoclaving before they are introduced into the peritoneal cavity of the dog, the dog suffers no harmful effects. Andrews and Hrdina reported that when 100 Gm. of fresh liver is finely ground and is then autoclaved and introduced into the peritoneal cavity, the dog dies in a few hours with toxemia caused by the Welch bacillus. They explained the difference in their results on the basis that the finely ground liver presents more surface for autolysis and absorption than the autoclaved chunks of liver and that the toxin thus produced is sufficient to cause the invasion of the peritoneal cavity by the Welch bacillus.

We found, contrary to the reports of Andrews and Hrdina, that 100 Gm. of fresh dog liver finely ground and sterilized by autoclaving usually does not cause death when injected aseptically into the dog's peritoneal cavity. It seemed logical to us, as mentioned earlier, that

the intraperitoneal implantation of preparations of liver, using ordinary surgical technic, might result in contamination by the normal flora of the abdominal wall. We therefore decided that the logical method of introducing the liver substance in an uncontaminated state would be by injection. The liver was therefore ground fine enough to be injected through a 15 gage needle.

Preparation of the Liver Substance.—In each case the dog from which liver was to be obtained was placed under general ether anesthesia and was prepared for aseptic surgical procedure. The abdomen was split open with hot wire cautery, and the abdominal wall was retracted. The portal vein and the inferior vena cava were ligated, and the liver, removed in a more or less bloodless state, was placed in a large, sterile Petri dish. The liver was immediately prepared as follows: The gallbladder, all the large veins, the connective tissue and the fat were dissected away and the remaining liver substance was passed through a sterile food-grinder. The ground liver was placed in 500 cc. Erlenmeyer flasks, each flask containing 110 Gm. of the ground liver. A small handful of glass beads and 100 cc. of physiologic solution of sodium chloride were added to each flask, and the lot was autoclaved at 15 pounds' (6.8 Kg.) pressure for fifteen minutes. The flasks were then removed from the autoclave and were placed in a mechanical shaker, after the cotton plugs were replaced with sterile rubber stoppers. After a vigorous shaking for forty minutes, the liver was filtered through gauze to remove the glass. The finely divided liver substance resulting was light brown and formed a suspension in the 100 cc. of physiologic solution of sodium chloride. The liver substance was put in 250 cc. Erlenmeyer flasks and was again autoclaved at 15 pounds' pressure for fifteen minutes. The preparation was then set in the icebox to await injection, the cotton plugs being first replaced with sterile rubber stoppers.

Experiment 1a.—Two dogs were prepared as for aseptic surgical procedure. A sterile 15 gage needle was pushed through the midline into the peritoneal cavity, and the liver substance was introduced by means of a 30 cc. syringe. We hoped in this way to introduce the needle without penetrating the muscle tissue.

In brief, the results of this experiment were as follows: Both dogs died approximately fifteen hours after the introduction of the liver substance. The dogs were examined with aseptic precaution, and specimens for smears and for cultures were taken of the peritoneal exudate and peritoneal surface. The autopsy observations on both dogs were typical. Needle puncture wounds were found penetrating the rectus muscle of each dog. In each case the abdomen contained about 500 cc. of thin bloody fluid. Both the liver and the spleen showed cloudy swelling but were not crepitant. There was moderate enteritis, most marked in the duodenum. The injected particles of liver were adherent to the omentum. The peritoneal surfaces were markedly injected and fiery red. The cultures and smears all yielded large, gram-positive, gas-forming anaerobes, staphylococci, streptococci and colon bacilli. Subsequent bacteriologic study of the gram-positive anaerobe revealed that it was identical with the anaerobic bacillus normally present in dog muscle. Tests on this organism for toxicity showed that it did not produce an exotoxin in vitro. We were still of the opinion that contamination of the injected liver substance occurred as the needle passed through the abdominal wall. With this in mind the experiment was modified as shown in experiment *1b*.

Experiment 1b.—Two dogs were prepared for injection as described in experiment *1a*. In this instance a slit was burned well through the skin, fascia and muscle in the midline of the dog's abdomen with a wire cautery. Care was taken

not to burn through the peritoneum. The 15 gage needle was then introduced through the cautery incision into the peritoneal cavity. The results of this experiment were different from those observed in experiment *1a*. One of the dogs lived indefinitely, and was used some months later in another experiment. The other dog died eleven days later of an extensive pneumonic process involving both lungs. Autopsy of this dog revealed that the abdominal cavity contained no gas or fluid. The liver and spleen were firm and were not crepitant. The lobes of the liver were adherent, with light, filmy adhesions. The omentum was the site of much black pigmentation and was bound to the site of the injection. The peritoneal surfaces were smooth and glistening. There was no sign of exudate on the peritoneal surfaces. A few particles of the injected liver substance were matted to the omentum, from which the normal fat was entirely absent, as if absorption had occurred. The pleural cavity contained from 25 to 30 cc. of dark bloody fluid. Both lungs were extensively involved with a pneumonic process. An account of experiments *1a* and *1b* will be found in table 1.

TABLE 1 (*Experiment 1*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Fresh Finely Ground Dog Liver Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	Smear	Culture	Survival	Organism	Exotoxin	Cause of Death
			Experiment 1a (Without the Cautery)			
76	Positive	Positive	15 hours	Muscle organism; staphylococcus; streptococcus; colon bacillus	None	General peritonitis
77	Positive	Positive	15 hours	Muscle organism; staphylococcus; streptococcus; colon bacillus	None	General peritonitis
			Experiment 1b (With the Cautery)			
597	None taken	None taken	Survived	None	None	Dog survived
598	None taken	None taken	11 days	None	None	Pneumonia; no peritonitis

We showed that when the liver was introduced aseptically by means of a small cautery incision through the skin, fascia and muscle and a needle puncture through the intact peritoneum, two dogs survived the injection, but that when the needle was inserted through the abdominal wall without cautery two dogs died of bacterial peritonitis. This observation led us to believe that finely ground fresh liver substance sterilized by autoclaving does not cause the death of the dog if the material is not contaminated in the process of its introduction.

The object of our next experiment was further to substantiate the thought that finely ground, sterile liver introduced in an uncontaminated state remained uncontaminated until absorbed. To prove this point it seemed necessary to remove samples of peritoneal exudate from the dog's peritoneal cavity for culture and smear from time to time following the introduction of the liver material. An attempt to aspirate peritoneal exudate through a 15 gage needle was more or less unsuccessful, but we found that by using a needle perforated in several places

near the beveled end peritoneal exudate can be aspirated successfully. This method was used in experiment 2.

Experiment 2.—Liver substance was injected into four dogs in the same manner as was described for experiment *1b*. As an added precaution against contamination the needle was heated red-hot before it was introduced through the cautery slit. The substance was successfully injected into three of the dogs in this manner. In the other dog a portion of the liver substance was inadvertently injected into the abdominal wall before it was seen that the needle had not completely entered the peritoneal cavity. The dogs were examined eighteen hours later. The dog with a portion of the liver preparation injected into the abdominal wall was dead and in rigor. The other three dogs were lying on their sides, breathing deeply. They were not comatose, however, and were able to stand when placed on their feet.

TABLE 2 (*Experiment 2*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Fresh, Finely Ground Liver Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	Samples Removed After 18 Hours	Survival	Autopsy
837	Smear and culture, negative	Killed after 2 weeks	No peritonitis; no fluid or gas in the peritoneal cavity; spleen and liver normal as to color and consistency; peritoneal surfaces smooth and glistening
838	Smear: positive for gram-positive bacilli and other contaminants Culture: positive for gram-positive bacilli and other contaminants	Found dead and in rigor in 18 hours	Some of the liver substance was injected by mistake into the abdominal wall; as a result examination showed: right rectus muscle necrotic and blown up with gas; general peritonitis with gas and turbid brown fluid in the peritoneal cavity, caused by direct extension of the infection through the peritoneal puncture
839	Smear and culture, negative	Alive after 6 months	Not killed
840	Smear and culture, negative	Killed after 3 months	No peritonitis; peritoneal surfaces smooth and glistening; liver and spleen normal as to color and consistency; a few filmy adhesions between the lobes of the liver

After the intracutaneous injection of a 1 per cent solution of procaine hydrochloride as an anesthetic, a specimen of peritoneal exudate was aspirated from each dog for culture and smear. To obtain the fluid a perforated 15 gage needle was introduced with the same cautery technic employed in the original injection. The peritoneal exudate of the living dogs was clear and blood-tinged, while that of the dead dog was turbid and dark brown. All cultures and smears of the peritoneal exudate of the living dogs were negative for bacteria, while both the smear and the culture of the peritoneal exudate of the dead dog yielded a gram-positive, gas-forming anaerobe which proved on further study to be the organism normally present in the muscle.

Autopsy of the dead dog revealed the right rectus muscle to be necrotic and blown up with gas. There was generalized peritonitis. The liver and spleen were not crepitant, although there were gas and a quantity of fluid in the peritoneal cavity. The three living dogs continued to improve and were able to partake of food and water on the third day. At the end of forty-eight hours an attempt was made to aspirate some of the peritoneal exudate from one of the dogs for smear

and culture, but no fluid could be obtained from the peritoneal cavity. One of the dogs was killed two weeks following the implantation of the liver substance. The general condition of the dog was good. Examination revealed complete healing of the cautery wounds in the abdomen. The peritoneal surfaces were smooth and glistening. There were no signs of peritonitis. The liver and spleen were normal as to color and consistency. The only evidence of the previously injected liver substance was an occasional minute particle caught in the omentum. Light, filmy adhesions were found between the lobes of the liver and between the liver and the diaphragm. The other two dogs were kept under constant observation, and except for a tendency to become extraordinarily fat no other observations of clinical interest were noted. One of the dogs was killed three months following the implantation of the liver. Autopsy revealed essentially a normal peritoneum. The light, filmy adhesions found in the first dog were between the lobes of the liver and between the liver and the diaphragm. There was a great deal of fatty infiltration about the viscera. The omentum was completely regenerated and contained a few areas of brownish pigmentation. The other dog was alive and apparently normal six months after the introduction of the liver substance. Table 2 gives an account of the experiment.

In experiment 2 we found that in three dogs 100 Gm. of fresh autoclaved liver, when injected aseptically into the peritoneal cavity, did not cause death. The material made the animal ill for a few days. However, one dog (838) in the series died, and in this case there was evidence of bacterial peritonitis associated with the infection in the wound caused by injecting the material into the abdominal muscles. The infection was due to organisms normally found in the abdominal wall of the dog. At autopsy we found the needle puncture wound digested and the infection extended into the peritoneal cavity. Obviously the material forms an ideal culture medium and when contaminated in any way causes death in a manner similar to that observed when fresh liver containing its normal flora is introduced into the peritoneal cavity. We have shown, however, that when 100 Gm. of fresh, finely ground, autoclaved liver is injected intraperitoneally in an uncontaminated state it remains sterile until absorbed and will not cause the death of a normal, healthy dog.

EXPERIMENTS WITH INCUBATED LIVER

Andrews and Hrdina reported toxemia caused by the Welch bacillus as a terminal event after the intraperitoneal introduction of dog liver which had been incubated and then sterilized by autoclaving. In an effort to substantiate these observations we conducted a series of experiments. The technic employed in injecting the liver substance and in aspirating the peritoneal exudates for bacterial smear and culture was the same as that employed in experiment 2.

Preparation of Incubated Liver.—We wish to point out that the nature of the incubated liver substance is different according to whether it is incubated with only the normal flora present or before incubation is contaminated with other

bacteria. The livers were removed from dogs in the same bloodless, aseptic manner described earlier in this paper. The linen, grinder, physiologic solution of sodium chloride and instruments and everything coming in contact with the liver were autoclaved. The technician was gowned, gloved and masked as for an aseptic surgical procedure. As an added precaution the livers were thoroughly scalded with autoclaved distilled water just before they were ground and placed in the sterile Erlenmeyer flasks. Three preparations of the incubated liver were made. One preparation was incubated for twenty-four hours, another for forty-eight hours and the third, for seventy-two hours. Sterilization in the autoclave, shaking, filtering and resterilization in the autoclave were done in the same manner as described for the preparations of fresh liver.

As was mentioned previously, the anaerobic bacterial flora of the normal adult dog liver enters actively into the digestion of the liver substance when the liver is incubated. Digestion is rapid, great quantities of gas being produced in twenty-four hours. The process continues for forty-eight hours and more but in most cases is complete in seventy-two hours. After autoclaving the material is dark brown with a pungent odor that is not putrefactive unless the liver has been contaminated with extraneous bacteria before incubation.

Experiment 3.—Four dogs were used in this experiment. One hundred grams of ground liver incubated for twenty-four hours and sterilized by autoclaving was injected intraperitoneally into each dog. Eighteen hours later two dogs were dead and the other two were prostrate and dyspneic. One of the dead animals showed rigor and too much postmortem change to justify any bacteriologic study. In the other it was apparent that death was recent, and material for smears and culture was taken from the peritoneal exudate of this animal. No gram-positive bacteria were found on the smear, but the culture was positive for gas-forming bacilli after incubation for eighteen hours at 40 C. Subsequent study and tests for toxicty on the gram-positive organism in this culture proved that it was the organism normally present in the muscle and that it did not produce an exotoxin in vitro.

Samples of the peritoneal exudate were removed from the two living dogs fourteen hours after the introduction of the liver material. All the smears and cultures of these specimens of peritoneal exudate were negative for bacteria. One of these two dogs was found dead nine hours later, twenty-three hours after the liver was injected. A sample of peritoneal exudate was removed from the other dog twenty-three and a half hours after the injection of the liver material. The dog was prostrate and more or less comatose at this time. Both the smear and the culture were negative for bacteria. When the dog was examined fourteen hours later his condition was much improved, and no sample of peritoneal exudate was taken. Six weeks later the dog was still living but was gaunt and emaciated. The dog died four or five days later and was cremated by an inexperienced caretaker before an autopsy could be performed.

The smears of the peritoneal exudate of dogs into which was injected the liver substance which was incubated are more or less difficult of interpretation; sterilization in the autoclave, although it kills the bacteria does not cause the disintegration of the bacterial bodies. Consequently all the smears of the peritoneal exudate of dogs into which this material was injected were positive for bacterial forms. These forms, however, stained gram-negative, had fuzzy outlines and were granular. If stains are made of the incubated liver preparation immediately after it is autoclaved, many of the bacterial forms stain gram-positive. After a week or so in the icebox these bacterial forms always take a gram-negative stain. We

interpreted as positive those smears which showed the presence of large, clearcut bacterial bodies which stained a definite gram-positive, or any stained smear was considered positive which showed the presence of staphylococci, streptococci or colon bacilli.

Typical postmortem observations on the dogs which died as the result of the intraperitoneal injection of the incubated liver preparations were as follows: The abdomen contained about 500 cc. of thin bloody fluid. The injected liver particles were caught in the omentum. The omentum and all the peritoneal surfaces were markedly congested and fiery red. There was no free gas in the peritoneal cavity. The liver and spleen showed cloudy swelling but were not crepitant. There was severe enteritis in the entire alimentary tract, most severe in the duodenum. The intestines, stomach and urinary bladder were usually contracted. The abdominal wall was edematous and the superficial veins were engorged with blood. An account of the experiment is given in table 3.

TABLE 3 (*Experiment 3*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Finely Ground Liver Incubated for Twenty-Four Hours and Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	First Sample	Subsequent Samples	Survival	Autopsy
841	14 hours: smear and culture negative	None taken	Dead and in rigor in 23 hours	No examination
842	Smear and culture not made	.....	Dead and in rigor in 12 hours	No examination
843	14 hours: smear and culture negative	23½ hours: smear and culture negative	Six weeks	Dog was cremated before autopsy could be done
844	12 hours: smear and culture, positive for gram-positive bacilli and other contaminants	.....	Dead in 12 hours; rigor had not set in	Abdomen contained about 500 cc. of blood-tinged fluid; no free gas in the abdomen; liver and spleen not crepitant; marked enteritis

Experiment 3 proved that 100 Gm. of ground liver incubated for twenty-four hours and sterilized in the autoclave is much more toxic to the dog than ground fresh autoclaved liver. The incubated liver usually causes the death of the dog in a few hours, although in this experiment one of the animals survived the injection for about six weeks.

We were of the opinion that the dogs into which this material was injected did not have bacterial peritonitis before they died, although the experiment did not definitely prove this. All the smears and cultures of the peritoneal exudate removed from these dogs before death were sterile. It seemed that the bacterial invasion of the peritoneal cavity occurred only after the dog died, but in order to be sure of this it was obvious that a more careful watch of the dogs was necessary, for the purpose of culturing the peritoneal exudate at the time of death. To do this and at the same time to see if the forty-eight hour incubated liver substance was more toxic than the twenty-four hour incubated liver, experiment 4 was carried out.

Experiment 4.—Three dogs were used. The experimental methods and observations were identical with those employed in experiment 3, except that in this instance ground liver which had been incubated for forty-eight hours and then sterilized by autoclaving was injected intraperitoneally. All three dogs died as the result of the injection. One of the dogs died twelve hours after the injection; one from eighteen to twenty-one hours after the injection, and the third, twenty-two hours after the injection. Cultures and smears of the peritoneal exudate removed from the peritoneal cavities of the three dogs twelve hours after the injection of the liver material were all negative for bacteria. One of the dogs died as the exudate was being removed from the peritoneal cavity. One of the remaining dogs died eight hours later before a second sample of exudate could be taken. A sample of peritoneal exudate was removed from the other dog just a few minutes before the dog died. The culture and smear of this sample were both negative. An account of the experiment is given in table 4.

TABLE 4 (*Experiment 4*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Finely Ground Liver Incubated for Forty-Eight Hours and Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	First Sample	Subsequent Samples	Survival	Autopsy
845	12 hours: smear and culture, negative*	.....	12 hours	No bacterial peritonitis; no gas in the peritoneal cavity; marked enteritis; about 500 cc. of blood-tinged fluid in the peritoneal cavity
846	12 hours: smear and culture, negative	None taken	Dead and in rigor in 20 hours	No examination
847	12 hours: smear and culture, negative	22 hours: smear and culture negative*	22 hours	Observations same as those for dog 845

* Sample of peritoneal exudate was removed as the dog was dying.

In experiment 4, smears and cultures of specimens of peritoneal exudate from the three dogs taken twelve hours after the injection of the liver substance were all negative for bacteria. In the case of two dogs smears and cultures of specimens taken at the time of death were likewise negative. There was no reason to believe that bacterial peritonitis developed before death.

It was evident that this material was much more toxic to the dog than the liver incubated for twenty-four hours. The dogs were obviously in a greater state of shock. In an effort to determine whether or not a still more toxic material would alter the bacteriologic results, liver incubated for seventy-two hours was injected into four dogs. This was experiment 5.

Experiment 5.—Ground liver incubated for seventy-two hours and sterilized by autoclaving was injected intraperitoneally into four dogs. The technic was the same as that employed in the preceding experiments with incubated liver. One dog was found dead five hours following the injection. Both the culture and the smear

of the peritoneal exudate contained gram-positive bacteria, staphylococci, streptococci and colon bacilli. The gram-positive organism was not Cl. Welchii.

One dog was prostrate and comatose in five hours. Both the culture and the smear of the peritoneal exudate removed at this time were negative for bacteria. One-half hour later, as the dog was dying, a second specimen of the peritoneal exduate was removed. The culture and smear of this specimen were likewise negative. A third sample was removed one-half hour post mortem. This sample was negative for bacteria on culture and on smear.

The other two dogs were prostrate, but reacted and were therefore kept under observation. Twenty-four hours after the injection of the liver material samples of peritoneal exudate were removed from both dogs. Both the smear and the culture of the peritoneal exudate removed from one of the dogs were negative. A sample of peritoneal exudate was removed from the same dog six hours later.

TABLE 5 (*Experiment 5*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Finely Ground Liver Incubated for Seventy-Two Hours and Sterilized by Autoclaving Was Injected Intraperitoneally*

Dog	First Sample	Second Sample	Third Sample	Survival	Autopsy
849	5 hours: smear and culture, positive; dog dead	1½ hours post mortem: smear and culture, positive	None taken	Found dead in 5 hours; no rigor	No gas in the peritoneal cavity; liver and spleen not crepitant; about 300 cc. of bloody fluid in the peritoneal cavity; much injection of the peritoneal surfaces; marked enteritis
850	24 hours: smear, negative; culture, positive	27 hours: smear, negative; culture, positive*	1½ hours post mortem: smear and culture, negative	27 hours	Same as for dog 849
851	24 hours: smear and culture, negative	30 hours: smear and culture, negative	1½ hours post mortem: smear and culture, positive	35½ hours	Same as for dog 849
852	5 hours: smear and culture, negative	5½ hours: smear and culture, negative*	½ hour post mortem: smear and culture, negative	5½ hours	Same as for dog 849

* This sample of peritoneal exudate was removed as the dog was dying.

It was likewise negative for bacteria. Five hours after the removal of the second sample the dog died. A third sample of peritoneal exudate was removed one and one-half hours post mortem. Both the smear and the culture of this sample of peritoneal exudate were positive for bacteria of many kinds.

The observations on the remaining dog of the series were unusual. Three samples of peritoneal exudate were removed. The first sample was removed three hours before death, the second as the dog died, and the third one and one-half hours post mortem. The smears were all negative for bacteria. Both cultures taken before death were positive for gram-positive anaerobes, staphylococci and streptococci, while the third culture, taken one and one-half hours post mortem, was negative for bacterial growth. This unusual result could be explained only on the grounds of contamination. The results of this experiment are found in table 5.

The experiments with incubated liver showed that dogs always die following the intraperitoneal injection of this preparation, usually in a

few hours. The peritoneum of several of the dogs into which the incubated liver was injected was shown by culture and by smear of the peritoneal exudate to be sterile at death. On the other hand, the peritoneal exudate of several of the dogs was shown by culture to be contaminated with gram-positive, gas-forming anaerobic bacilli, staphylococci, streptococci and colon bacilli. The essential fact is that preparations of fresh liver which are allowed to incubate from twenty-four to seventy-two hours before being sterilized contain in themselves some toxic factor which is sufficient to cause the death of the dog in every instance. When a sample of peritoneal exudate yielded a gram-positive, gas-forming anaerobe, subsequent isolation and study of the organism proved it in most instances to be the organism commonly found in the muscle of normal adult dogs. In no instance were we able to isolate Cl. Welchii or any organism that produced an exotoxin in vitro. The fact that smears were repeatedly negative for living bacterial forms, that positive cultures were usually associated with common contaminants and that our observations were variable led us to believe that contamination was still a great factor in our results. It is true that when fresh autoclaved liver was injected subsequent cultures of the peritoneal exudate were almost uniformly negative, indicating that under these conditions the technic of cautery and needle puncture was adequate to prevent contamination. When, however, a dog was prostrated and dying from the shock of the highly toxic incubated and autoclaved liver, the peritoneal cavity was more easily infected by the insertion of a large needle through the abdominal wall. This belief was strengthened by the observation that the toxic incubated suspensions of liver caused marked venous engorgement and edema of the abdominal wall. Cautery burns and perforations by a hot needle of this highly vascular and edematous tissue could be the source of bacterial contamination of the peritoneal cavity. Some procedure for introducing the material into and aspirating peritoneal fluid from the abdominal cavity with more strict bacteriologic technic seemed necessary. Therefore, a method was devised, as used in experiment 6.

Experiment 6.—By careful aseptic surgical procedure a small area of the peritoneum of the dog was exposed through an incision in the lower right quadrant of the abdomen about 1 inch (2.5 cm.) from the midline. The peritoneum at this point is continuous with the aponeurosis of the internal oblique muscle and forms a tough, resistant structure. The skin was opened with a cautery, and the muscles were separated with as little trauma and bleeding as possible. The instruments used for the operation were thoroughly phenolized as well as boiled before they were used. The exposed peritoneum was grasped with two mosquito forceps and lifted out of the peritoneal cavity. A purse-string suture of sterile, strong silk was sewed in the peritoneum about the clamps. A small incision about 3/8 inch (0.9 cm.) long was made through the peritoneum inside the purse-string suture. The edges of the cut peritoneum were grasped with mosquito forceps and turned outward. The end of a sterile glass tube especially designed for the pur-

pose was inserted through the opening, and the peritoneum was tied tightly about the first constriction of the tube. The tube was pulled outward, and the peritoneum was again tied securely about the second constriction. This procedure firmly anchored the tube to the peritoneum and made a bacteria-tight closure about the tube. The abdominal incision was then carefully closed about the tube, care being taken not to tie off or devitalize any muscle tissue. Figure 1 illustrates the nature of the tube and the manner of its insertion. The tube can easily be made from glass test tubes, and by first searing the vaccine bottle stopper with a wire cautery any number of samples of peritoneal exudate can be removed in an uncon-

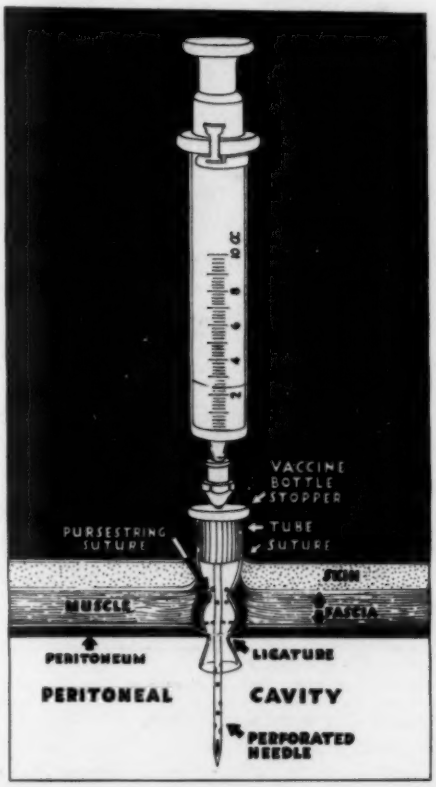

Fig. 1.—A diagram showing the insertion of the tube used to obtain uncontaminated samples of peritoneal exudate from the dog's peritoneal cavity.

taminated state. Likewise, any material that can be injected through a hypodermic needle can be introduced intraperitoneally in an uncontaminated state. This arrangement has proved ideal for any study of the peritoneal exudate of dogs taking place over a period of from thirty to forty-eight hours following the placing of the tube. After a time the peritoneum devitalized by the grasp of the retaining sutures will slough, and the point of the insertion of the tube will no longer be bacteriologically tight.

By using this technic the following experiment was carried out: The tube was anchored to the peritoneum of three dogs in the manner described. One hour after

the insertion of the tube 100 Gm. of ground sterile liver incubated for seventy-two hours was injected into one dog. Liver incubated for forty-eight hours was injected into another dog, and liver incubated for twenty-four hours was injected into the third. The preparation of the liver was the same as that described earlier in this paper. Samples of peritoneal exudate were removed at one and a half and two hour intervals until the death of the dogs. The dogs were kept in a lethargic and painless state by the intramuscular injection of small amounts of morphine and sodium amytal. In brief, the results of the experiment were as follows:

The dog into which the liver, incubated for seventy-two hours, was injected died in nine hours. During this time five consecutive samples of the peritoneal exudate

TABLE 6 (*Experiment 6*).—*Bacteriologic Study of Peritoneal Exudates, Samples of Which Were Removed Through the Tube Described in Experiment 6*

Dog	Liver Incubated for	Samples	Time Taken	Smears	Culture
951	72 hours	1	2 hours	Negative	Negative
		2	3½ hours	Negative	Negative
		3	5 hours	Negative	Negative
		4	6½ hours	Negative	Negative
		5	8 hours	Negative	Negative
		6*	9 hours	Negative	Negative
		7†	10 hours	Negative	Negative
		8‡	11 hours	Negative	Positive
954	48 hours	1	15 minutes	Negative	Negative
		2	2½ hours	Negative	Negative
		3	4½ hours	Negative	Negative
		4	6½ hours	Negative	Negative
		5	8½ hours	Negative	Negative
		6	10½ hours	Negative	Negative
		7	12½ hours	Negative	Negative
		8	14½ hours	Negative	Negative
		9	16½ hours	Negative	Negative
		10	19 hours	Negative	Negative
		11	22 hours	Negative	Negative
		12*	24 hours	Negative	Negative
		13†	25 hours	Negative	Negative
955	24 hours	1	15 minutes	Negative	Negative
		2	2½ hours	Negative	Negative
		3*	5½ hours	Negative	Negative
		4†	6½ hours	Negative	Positive
		5‡	7½ hours	Negative	Positive
		6§	9½ hours	Negative	Positive

* This sample was removed as the dog died.
† This sample was removed one hour post mortem.
‡ This sample was removed two hours post mortem.
§ This sample was removed four hours post mortem.

were removed for bacteriologic smear and culture. One sample was taken as the dog was dying. Two samples taken subsequently were removed one and two hours post mortem. All smears, including the one taken two hours post mortem, were negative for bacterial growths. Cultures of the first seven samples of peritoneal exudate removed, including the one removed one hour post mortem, were also negative. Culture of the sample of peritoneal exudate removed two hours post mortem was positive for bacterial growth after incubation for eighteen hours at 40 C. Subsequent study of the organism showed that it was present in the exudate in pure culture and that it was identical with the organism commonly found in dog muscle.

The second dog, into which was injected liver material incubated for forty-eight hours, lived for twenty-four hours. During this time thirteen consecutive samples of the peritoneal exudate were removed. All the smears of these samples were

negative for bacteria. Cultures taken of the peritoneal samples were likewise negative for bacterial growth. The last sample was removed one hour post mortem.

The third dog, into which was injected liver material incubated for twenty-four hours, lived for five and one-half hours. Three samples of peritoneal exudate were removed from this dog while it was still living, the third sample being removed as the dog was dying. Three samples taken subsequently were removed one, two and four hours post mortem. Smears of all six of the samples were negative for bacteria, while cultures of the three samples removed post mortem showed bacterial growth. Bacteriologic study of the positive cultures showed a gram-positive anaerobe that existed in the peritoneal exudate in pure culture. This organism was likewise identical with the organism normally present in the muscle tissue of adult dogs. An account of the experiment is given in table 6.

The technic described in experiment 6 enabled us to collect numerous sterile cultures from the peritoneal exudate of dogs dying as a result of the toxic injection. With these meager data we are not prepared to say that all normal dogs have a sterile peritoneum. We have proved, however, that the incubated liver is sufficient in itself to cause the death of the dog. We believe that any bacterial growth found in the peritoneal cavity in the experiments reported earlier is probably due to contamination. We seriously doubt the possibility of the incubated liver material ever causing the antemortem invasion of the peritoneal cavity by bacteria. We are certain that in these experiments it has not caused the invasion of the peritoneal cavity by Cl. Welchii during life. It seems that dogs receiving ground, incubated, sterile liver intraperitoneally die with a sterile peritoneum. In two of the dogs in experiment 6 the peritoneum remained sterile as long as one hour post mortem.

EXPERIMENTS WITH STERILE SOLUTIONS OF BILE SALTS

Rewbridge and Andrews, Rewbridge and Hrdina have reported that a 10 per cent sterile solution of bile salts (5 cc. per kilogram) is uniformly fatal to the dog when it is introduced intraperitoneally. In their opinion death is due to peritonitis caused by the Welch bacillus induced by the intraperitoneal implantation of the bile salt solutions. It has long been known that bile salts are toxic per se, but Rewbridge reported that the bile salts are not absorbed into the blood stream to toxic levels sufficient to cause the death of the dogs. He concluded that death is caused by the devitalizing action of the bile salts on the peritoneum, bringing about a subsequent invasion of the peritoneal cavity by the Welch bacillus, which he considered to be a normal inhabitant of dog tissues. Our observations on this phase of the subject are the result of experiment 7.

Experiment 7.—As we were uncertain whether autoclaving would affect the toxicity or otherwise change the character of the bile salts, we prepared two

different solutions. One solution was sterilized by passing it through a Berkefeld candle, and the other, by autoclaving. Both preparations were proved sterile by culture. A 10 per cent solution of bile salts was prepared by dissolving equal quantities of sodium taurocholate and sodium glycocholate in distilled water. Andrews, Rewbridge and Hrdina having reported that 5 cc. per kilogram of such a solution was uniformly fatal to the dog, we used that amount in our experiments.

Four dogs were prepared in the usual way for aseptic surgical procedure. In two of the dogs a glass tube was anchored to the peritoneum in the manner described in experiment 6. Each of these dogs received an intraperitoneal injection of the bile salt solution through the tube. In one case, bile salts sterilized by passage through the Berkefeld filter were used, and in the other, autoclaved bile salts.

With the thought that in case the animal survived the presence of the tube might vitiate later observations, we employed a different technic in injecting the solution into the other two dogs. In these animals the peritoneum was exposed, but instead of the tubes being anchored a 15 gage needle was inserted and tied with a purse-string suture to the peritoneum. After the bile salt solution was injected the needle was withdrawn, and the perforation of the peritoneum was closed by the suture. The incisions were then repaired. The four dogs were kept under constant observation.

The results of this experiment were as follows: All four dogs died, those receiving the bile salt solutions sterilized by passage through the Berkefeld filter dying first. Five samples of peritoneal exudate were removed from the dog which had received through the tube the bile salt solution sterilized by filtration. The first sample was taken one hour following the injection and the second, four hours later as the dog was dying; the other three samples were removed one, two and three hours post mortem. No bacteria of any kind were found on stained smears of these samples. Cultures of the first three samples, including the one taken one hour post mortem, were negative for bacterial growth. Cultures of the last two postmortem specimens were positive for bacterial growth, even though no bacteria were seen in the smears.

Three samples of peritoneal exudate were removed from the dog which had received the autoclaved bile salt solution through the tube. This dog survived the injection twenty hours. The first sample was removed five hours after the injection of the bile salts, the second four hours later and the last one and one-half hours post mortem. Smears of the first two samples revealed an occasional gram-positive rod, but no other bacteria. A smear of the sample taken post mortem revealed bacteria of many kinds. Cultures of all three samples showed a growth of different kinds of organisms. This result was explained when the dog was examined at autopsy. At this time we found the stomach full of bones, with a perforation in the lower border of the fundus about 1 cm. in diameter. This had the appearance of an old ulcer, and microscopic section confirmed this diagnosis. Obviously this perforation of the stomach contaminated the peritoneal cavity. For that reason no effort was made to isolate or to determine the morphology of the bacteria present in the cultures. We mention these findings only to complete the series.

The two dogs which received the injection of the bile salt solution through the needle were closely watched in order to obtain cultures at the time of death. In each instance, as the dog was dying a needle was inserted through a small cautery wound in the abdominal wall and samples of peritoneal exudate were removed.

Cultures and smears of both these samples were negative for bacteria. In general, these dogs presented the same picture of prostration and shock as was observed when the incubated liver preparations were injected.

Autopsy observations on the dogs were similar, with the exception of those on the dog with the perforated stomach. In this animal there was a large amount of brownish-red turbid fluid and free gas in the peritoneal cavity. The other three dogs presented the following findings: The peritoneum and omentum were moderately injected. The peritoneal cavity contained about 500 cc. of bright red fluid. The liver and spleen were swollen but firm and not crepitant. Enteritis

TABLE 7 (*Experiment 7*).—*Bacteriologic Study of Peritoneal Exudate of Dogs Into Which Sterile Solution of Bile Salts Was Injected Intraperitoneally*

Dog	Samples	Smears	Culture	Survival	Autopsy
		Solution Sterilized by Autoclaving			
959	1 hour	Positive	Positive	20 hours	Congestion of the peritoneal surfaces and omentum; 500 cc. of brownish-red turbid fluid in the peritoneal cavity; marked enteritis in the ileum, less marked in the rest of the gastro-intestinal tract; distended gallbladder; perforated ulcer in the lower margin of the fundus of the stomach
	5 hours	Positive	Positive		
	1½ hours post mortem	Positive	Positive		
961	Removed as dog died	Negative	Negative	8 hours	Moderate congestion of the peritoneal surfaces and omentum; 500 cc. of bright red fluid in the peritoneal cavity; marked enteritis in the ileum, less marked in the rest of the gastro-intestinal tract; marked contraction of the ileum; distended gallbladder; laked blood in the peritoneal cavity
		Solution Sterilized by Berkefeld Filter			
960	1 hour	Negative	Negative	5 hours	Same as for dog 961
	5 hours	Negative	Negative		
	1 hour post mortem	Negative	Negative		
	2 hours post mortem	Negative	Positive		
	3 hours post mortem	Negative	Positive		
962	Removed as dog died	Negative	Negative	.....	Same as for dog 961

was marked in the ileum, but was less marked in the rest of the gastro-intestinal tract. The ileum was tightly contracted throughout its entire extent. The jejunum and duodenum were moderately distended with gas. The large intestine was moderately contracted. The gallbladder in every instance was swollen and tense with bile. There was no gas present in the peritoneal cavity. It interested us to note that within one-half hour after the injection of the bile salts the peritoneal exudate was bright red due to laking of the extravasated blood. An account of the results of this experiment is given in table 7.

Experiment 7 proved that this concentration of equal amounts of the two bile salts, when injected into the peritoneal cavity of the normal adult dog, will cause death in a few hours. In our opinion, this observation has no clinical significance. A 10 per cent solution of the two

bile salts is in no way comparable to bile which one may encounter in the peritoneal cavity under ordinary conditions.

The fact that the dogs die with a sterile peritoneum is conclusive evidence that death is not due to peritonitis caused by the Welch bacillus and that the peritoneum is not invaded by bacteria of any kind as a result of the presence of bile salts per se. In view of Rewbridge's conclusion that in these concentrations bile salts are not absorbed into the blood stream to lethal levels, an interesting question arises as to what is the mechanism of death. For the present, we state merely that death occurs without bacterial peritonitis.

COMMENT

In the experiments described we made many observations which do not confirm the reports of previous investigators. Andrews, Rewbridge and Hrdina stated that in all phases of this complex experimental problem death is due to toxemia caused by the Welch bacillus. They employed the terms "autolytic peritonitis" and "in vivo autolysis" to designate conditions in which the sterile preparations of liver and of bile salts cause death when introduced intraperitoneally. At autopsy on their animals they found violent bacterial peritonitis, with the formation of gas in the peritoneal cavity as well as in the liver and other tissues. They concluded that the toxic substances injected, even though sterile, caused an autolytic process that resulted in an invasion of the peritoneal cavity by the Welch bacillus, which they stated is normally present in dog tissue.

We have shown that the liver of the normal dog contains an anaerobic bacterial flora and that when pieces of the liver are introduced into the peritoneal cavity of the dog, death results in a few hours and is associated with bacterial peritonitis. When, however, fresh liver is finely ground and sterilized by autoclaving it may be placed in the peritoneal cavity without causing death, provided it is not contaminated. If, on the other hand, the fresh liver is allowed to incubate before being sterilized in the autoclave, bacterial decomposition produces a highly toxic substance, the intraperitoneal injection of which causes death in a few hours, with the animal manifesting a state of profound shock. We have shown that death occurs without bacterial growth in the peritoneal cavity. The same observation was made in the experiments on the intraperitoneal injection of bile salts. These differences have been demonstrated by a careful examination of the peritoneal exudate and postmortem observations.

The peritoneal exudate in all dogs in which there was no contamination was negative for bacteria and frequently remained so until one or two hours after death. Figure 2 clearly shows the difference between

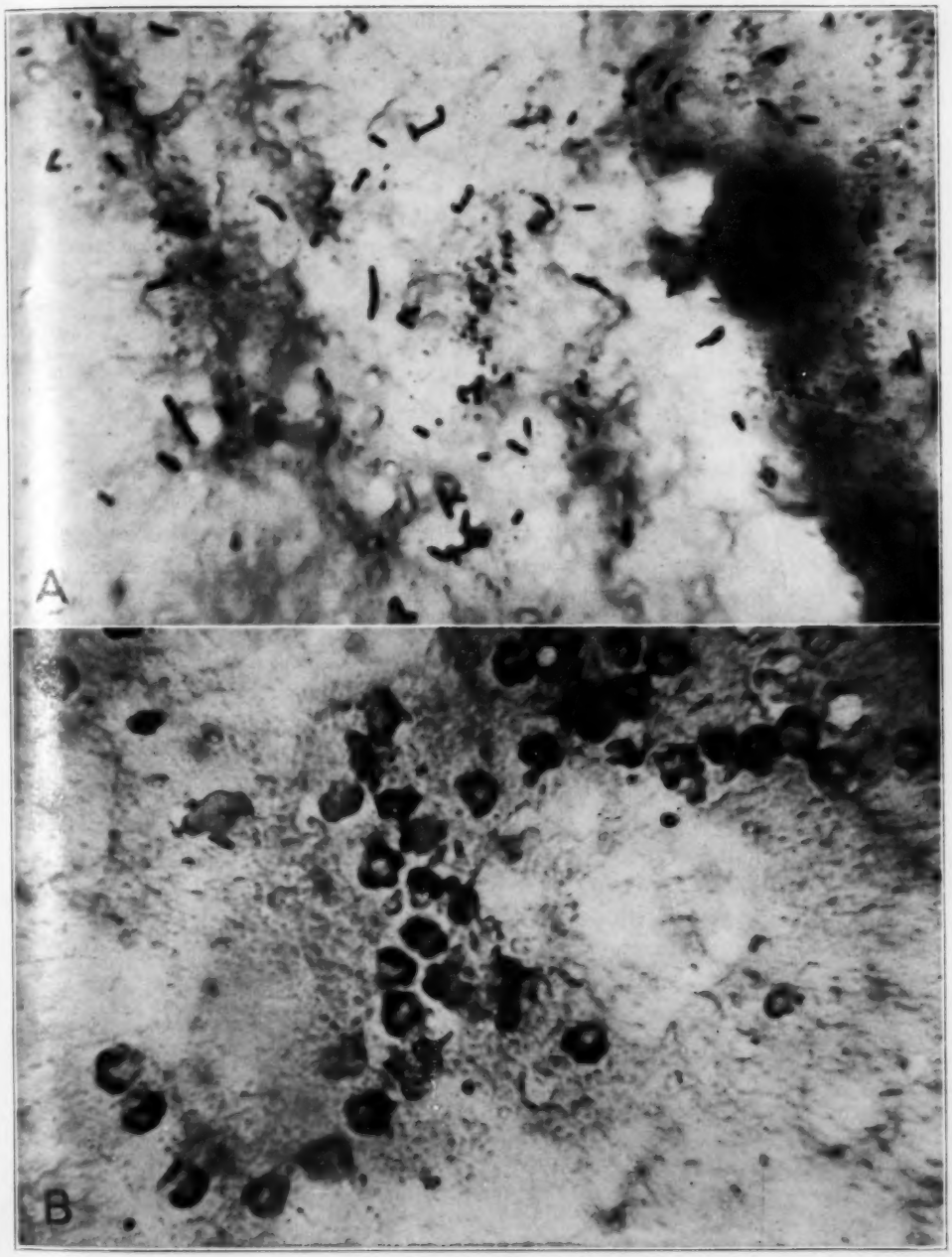

Fig. 2.—Photomicrographs of stained smears of samples of peritoneal exudate. *A* shows an example of bacterial peritonitis and *B*, an example of sterile peritonitis.

this type of sterile peritonitis and the typical bacterial peritonitis which occurs when bacteria are introduced into the peritoneal cavity. The difference becomes even more evident at autopsy. In the dog dying with a sterile peritoneum there was present a large quantity of thin blood-tinged fluid. The serous surfaces were fiery red. The liver and spleen were grossly normal and contained no gas, nor was gas present in the peritoneal cavity. There was marked hemorrhagic enteritis throughout the entire intestinal tract. In dogs in which death was associated with bacterial peritonitis, the picture at autopsy was similar except that the fluid present was turbid and foul and gas was present in varying amounts. The organisms found in the smears and cultures of the samples of exudate from these dogs were of many kinds, the anaerobic group of which at no time included Cl. Welchii. The anaerobic organisms present were invariably large, gram-positive, gas-forming saprophytes which exist in the normal tissues of the adult dog. In our experiments, these organisms have not produced a demonstrable exotoxin in vitro as compared with Cl. Welchii and other pathogenic anaerobes. As previously reported, by using accepted bacteriologic methods of cultivation and tests for the presence of bacterial exotoxins, we have been able in all cases to demonstrate these exotoxins in the filtrates of organisms known to produce them. We wish to point out that the intravenous injection of from 10 to 20 cc. of protein filtrates into small animals is not an accurate test for the presence of an exotoxin.

We do not deny that under certain conditions these nonpathogenic organisms cause death when they gain access to the peritoneal cavity. We have found, however, that when the broth portion of a growing culture of these saprophytes is injected intraperitoneally, even in amounts of 35 cc., no noticeable harmful effect results, but if the meat from the bottom of the tubes is injected together with the organisms, the dog dies promptly of bacterial peritonitis. Cl. Welchii gives a different result. In this instance 35 cc. of the clear broth culture is sufficient to cause death as a result of general toxemia, even though peritonitis is not found at autopsy. This indicates that in the presence of some unabsorbable material which can serve as a culture medium, even nonpathogenic organisms cause fatal peritonitis, but when these organisms can be rapidly absorbed from the peritoneum, no harm results unless the organisms are highly virulent.

There is much confusion in the literature concerning the proper classification of gram-positive, gas-forming anaerobes. There seems to be a tendency to use the terms "Welch bacillus" and "gas bacillus" promiscuously. The gas-forming organism described by Welch, however, is definitely pathogenic and is characterized by the formation of

an exotoxin. We have observed an instance of so-called endogenous infection caused by a "gas bacillus" complicating embolic gangrene of the arm. In this case the tissue of the upper part of the arm and of the axilla, the neck and the wall of the chest were distended with gas, but the patient showed no evidence of toxemia and responded promptly to amputation of the arm with drainage of the crepitant tissue. We believe that such cases cannot be classified accurately as infections caused by Cl. Welchii, but are more probably due to nontoxic gas-forming saprophytes growing in devitalized tissue. During the World War, Weinberg and Séguin [8] made the distinction between gas gangrene with toxemia, jaundice and hemolysis and putrefactive gangrene with little or no systemic effect. The toxic "gas gangrene" was caused by three known anaerobic organisms, each of which produced a demonstrable exotoxin. The three organisms were Cl. Welchii, Clostridium oedematis and Clostridium oedematis-maligni. The putrefactive gangrene was caused by a host of unclassified saprophytes which thrive in dead or devitalized tissue, and it was early found that débridement and drainage were sufficient to stop their growth. Infections by the three aforementioned pathogenic members of the genus are usually fatal unless proper specific treatment is available.

In dogs, the putrefactive type of gangrene can be produced by the intramuscular injection of highly toxic liver preparations which devitalize tissue and serve as a culture medium for the saprophytes commonly present there. Even when growing in the skeletal muscle tissue of the dog they do not usually cause death, recovery occurring when the infection is drained, either spontaneously or by surgical intervention. The death which results when these organisms gain access to the peritoneum has already been discussed.

We are not in sympathy with the thought that intraperitoneal injection of sterile, though toxic, material causes an idiopathic bacterial invasion of the peritoneal cavity during life. When, by suitable technic, the material was kept sterile, the peritoneum remained sterile even though the material was sufficiently toxic to cause death.

We do not wish to state that the dog's peritoneal cavity is always sterile under normal conditions. Recently the work of Roberts, Johnson and Bruckner [9] has been brought to our attention. These authors reported that in the bacteriologic study of the peritoneal fluid obtained during two hundred and nine laparotomies in human subjects, 80 per cent of the specimens contained different kinds of bacteria. They pointed

8. Weinberg, M., and Séguin, P.: La gangrene gazeuse: bacteriologie, reproduction expérimentale, sérothérapie, Paris, Masson & Cie, 1918.

9. Roberts, K.; Johnson, W. W., and Bruckner, H. S.: The Aseptic Peritoneal Cavity: A Misnomer, Surg., Gynec. & Obst. **42**:752 (Dec.) 1933

out that the peritoneal cavity was contaminated equally often in the absence of inflammatory reactions as in cases of active inflammation and concluded that the term "the aseptic peritoneal cavity" is a misnomer. We make no effort to compare these observations with the results we are reporting, except to state that we have obtained sterile cultures from samples of peritoneal exudate of dogs when, and only when, a technic was devised to avoid contamination from the abdominal wall.

Our cultural methods, as previously reported, conform to the accepted methods of study of anaerobic bacteria. We have consistently produced the growth of many kinds of bacteria when the organisms gained access to the medium. We see no reason to question our results on this basis. A plausible explanation for the conflict in our results as compared to those reported by Andrews seems obvious. We have found that routine aseptic surgical technic is inadequate for bacteriologic studies in the dog.

CONCLUSIONS AND SUMMARY

1. The tissues of living dogs contain an anaerobic flora which is composed of several strains of unclassified, putrefactive, gas-forming saprophytes. We did not find Cl. Welchii.

2. One hundred grams of fresh, finely ground dog liver sterilized by autoclaving when injected intraperitoneally, does not cause death unless contamination occurs during or after injection.

3. When fresh liver containing its normal flora is placed in the peritoneal cavity, or when sterile suspensions of liver injected intraperitoneally become contaminated, death occurs and is associated with bacterial peritonitis.

4. One hundred grams of finely ground liver incubated for twenty-four, forty-eight or seventy-two hours and sterilized by autoclaving when injected intraperitoneally in an uncontaminated state causes death promptly in the dog. Death is not caused by bacterial growth in the peritoneal cavity.

5. The intraperitoneal injection of 5 cc. per kilogram of body weight of a 10 per cent sterile solution of the two bile salts is fatal in a few hours. Death is not caused by a bacterial growth in the peritoneal cavity.

6. Neither the sterile liver nor the bile salts per se cause an invasion of the peritoneal cavity by Cl. Welchii or by any other bacteria.

7. The various incubated preparations of liver and the sterile bile salts cause an intense irritation of the peritoneal surfaces, with much

extravasation of blood and fluids, and we believe the death of the dog to be associated with shock.

8. We have reported a method which has proved satisfactory in our hands for removing uncontaminated samples of peritoneal exudate from the dog's peritoneal cavity.

This work has been done under the supervision of Dr. W. D. Gatch. Assistance has been given us by Dr. Thurman B. Rice of the department of bacteriology and pathology and by Mr. Fred A. Miller and Mr. Galen Boring of the biologic department of the Eli Lilly Research Laboratories.

DEVELOPMENT AND TREATMENT OF PEPTIC ULCER

AN EXPERIMENTAL STUDY

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Numerous methods have been devised for the experimental production of peptic ulcer in animals. In these experiments, spontaneous experimental peptic ulcer was produced in an intestinal fistula that extended from a gastric pouch to the abdominal wall. This method permits the investigation of phases of the problem which have not heretofore been touched on. As the ulcers were completely removed from the main gastro-intestinal tract, many confusing factors could be eliminated. Furthermore, the ulcers were easily accessible, so that various types of treatment could be applied directly to their surface.

In a preliminary report I [1] outlined the factors that were responsible for the development of such an ulcer, the changes in the secretion in the pouch and a method of preventing or healing the ulcer. In this paper a more complete report will be made concerning the development of the ulcers, concerning mucosal susceptibility to the formation of the ulcers and concerning methods of treatment.

METHOD

Dogs were used in all of the experiments and were prepared according to the technic of Goldberg and Mann.[2] The operation was performed in two stages. The first stage consisted in resecting a loop of intestine from 10 to 15 cm. long. Intestinal continuity was reestablished by an end-to-end anastomosis. The distal end of the resected loop was then sutured to an opening in the stomach, and the proximal end was brought out through a stab wound in the abdominal wall. By arranging the transposed loop in this way, the peristaltic waves traveled toward the stomach, thus preventing leakage of the secretion from the pouch. The second stage was performed from three weeks to six months later, and consisted in dividing the stomach so that the portion of it that was drained by the intestinal fistula formed a gastric pouch (fig. 1).

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery. The work was done in the Division of Experimental Medicine.

1. Harper, F. R.: Development of Experimental Peptic Ulcer: Changes in Acidity and Treatment, Proc. Staff Meet., Mayo Clin. **7**:318 (June 1) 1932.

2. Goldberg, S. L., and Mann, F. C.: Preparing Pouches of the Fundus of the Stomach, Ann. Surg. **94**:953 (Nov.) 1931.

In order to determine the importance of gastric secretion in the development of spontaneous ulcer and the resistance of the various levels of the intestinal mucosa to the formation of ulcer, various preparations were made, using different parts of the stomach in combination with different levels of the intestine. Thus, pouches made from the cardiac, the pyloric or the fundic portion of the stomach were drained by fistulas from the ileum. Since the fundic portion of the stomach secretes the most acid, fistulas made from the jejunum and the duodenum were also used in draining the fundic pouches.

Three additional types of preparation were made that require special mention. Each of two dogs was prepared with a double fistula made from the ileum. This was arranged so that peristalsis in one of the fistulas would travel toward the stomach, whereas, in the other it would be directed away from the stomach. The pouch was made from the fundus of the stomach and included both of these

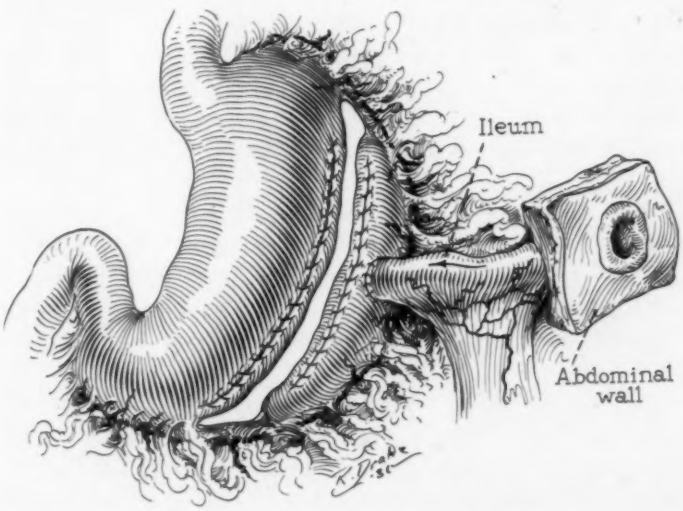

Fig. 1.—Formation of an isolated gastric pouch, second operation.

fistulas. In one dog a Pezzer catheter was inserted through the fistula into the fundic pouch, so that the mushroom-like end impinged on the walls of the pouch. This catheter was kept in place continuously after the second stage so that all of the secretion which left the pouch was carried out by the catheter and did not come in contact with the mucosa of the fistula. The secretion was collected in a balloon attached to the catheter. Another dog was prepared with a pouch made from the fundus of the stomach and a fistula from the jejunum. In this dog the nerve supply to the fistula was destroyed by stripping the mesenteric vessels.

In the case of each animal the weight was recorded and bleeding from the fistula or other changes were noted at regular intervals. These data were found to be important in determining the time when the ulcer began to develop. Studies of the secretion from the pouch were made every third or fourth day as the ulcer developed. The secretion was examined in a routine manner. The dog fasted for twenty hours before a series of observations was started. After a specimen was taken the dog was fed 100 Gm. of diced raw meat. The contents of the pouch

were then withdrawn at two hour intervals by means of a soft rubber catheter inserted into the pouch through the fistula. The dog was replaced in its cage between observations. These two hour specimens were taken over periods of eight, twelve or twenty-four hours. The amount and character of each specimen were recorded, and the p_H, the free and the combined acidity in terms of tenth-normal sodium hydroxide per hundred cubic centimeters, and the number of milligrams of total chlorine per hundred cubic centimeters of gastric secretion were determined.

Three substances were tried in treating the ulcers. Sodium bicarbonate was given by mouth and also injected into the pouch. Gastric mucin was introduced into the pouch in an attempt to heal the ulcer or to prevent its formation. Finally, an emulsion was prepared, using gelatin, acacia, olive oil and lecithin. Twenty cubic centimeters of this emulsion was introduced into the pouch twice daily during the time the ulcer was being treated.

Necropsy was performed on each animal, and gross and microscopic studies were made of all specimens. A sufficient number of animals was used to permit definite conclusions to be drawn.

RESULTS

A study of the results brought out several points in regard to the factors responsible for the development of this type of experimentally produced ulcer. In the first place, in no instance did an ulcer develop after the first stage of the operation, even though the animal was kept for a long time and catheters were repeatedly passed through the fistula. It was thus possible to rule out certain factors such as trauma, a faulty supply of blood and so forth.

When the fundus of the stomach was used in making the pouch, free acid was found in the secretion of the pouch and an ulcer formed in the fistula in each of the animals. However, if the cardiac or the pyloric portion of the stomach was used in making the pouch, free acid was not present in the secretion of the pouch and an ulcer did not form in the fistula. Furthermore, when the fistula was protected by constantly draining the secretion from the pouch through a Pezzer catheter, an ulcer did not form. These observations illustrate the significance of the chemical or acid factor in the development of ulcers.

As has been mentioned, each of two dogs was prepared with two fistulas draining a fundic pouch. In these dogs an ulcer did not develop in either fistula. In one of them, after more than ample time had been allowed for an ulcer to develop, one of the fistulous loops was removed and the abdomen was explored to make sure no ulcer existed in the other loop. Two weeks after the fistulous loop was removed, a perforating ulcer was found at necropsy in the remaining loop of the intestine. It may be that mechanical factors contribute to the development of such ulcers and that a second draining fistula eliminates these factors.

The series in which a loop of the intestine was used in combination with the fundic portion of the stomach illustrated the varied susceptibility of the mucosa of different regions of the intestine to the formation

of ulcer. When a portion of the ileum was used, the average length of time before perforation occurred was twenty-three days; when the jejunum was used, the average time was seventy-one days, and when the duodenum was used, ulcers formed but did not perforate. It was thus fairly well established that the vulnerability of the mucosa to the formation of ulcer becomes greater as the distance from the stomach is increased.

Fig. 2.—Ulcer in a fistula made from the ileum. Note the lack of resistance of the ileal mucosa to the formation of ulcer and that the ulcer does not begin at the line of suture.

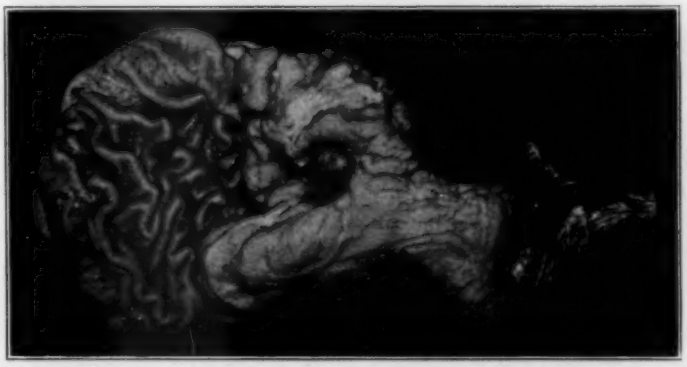

Fig. 3.—Chronic nonperforating ulcer in a fistula made from the duodenum.

There are several other points that should be mentioned in regard to the preparations. The size of the pouch apparently had no effect on the rate of development of the ulcer or on its size. Also, the length of the intestinal loop that was used in making the fistula did not influence the formation of the ulcer. In each case the ulcer was situated in the fistula, about 1 cm. from the line of suture that joined the fistula to the pouch. The ulcers which occurred in the fistulas made from the ileum were of the acute perforating type (fig. 2), whereas the ulcers in the fistulas made from the jejunum or from the duodenum resembled

chronic duodenal ulcers in man, as to both gross and microscopic appearance (fig. 3). Although the ulcers were entirely separate from the main part of the gastro-intestinal tract and did not come in contact with food, they had a very definite effect on the animals, the most striking effect being the rapid loss in weight, which amounted to from 1 to 6 Kg. On the other hand, the dogs actually gained weight on the same regimen when ulcers were prevented from forming. In addition to the loss of weight, definite symptoms developed as the ulcer became advanced, chief among which were loss of appetite and vomiting after eating. In the later stages the chlorides in the blood were reduced to from 280 to 300 mg. per hundred cubic centimeters. When a dog with a well developed ulcer was given 200 cc. of 10 per cent dextrose in 1 per cent saline

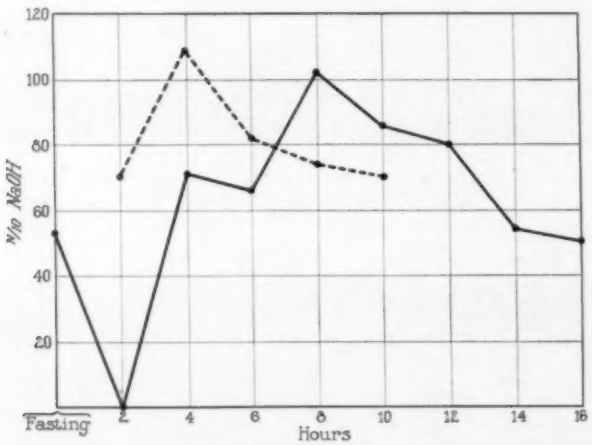

Fig. 4.—The effect of sodium bicarbonate on the acidity of the secretion from the pouch. The broken line represents the values for total acidity two days before sodium bicarbonate was given; the solid line, the values obtained after the administration of 1 Gm. of sodium bicarbonate per kilogram with a test meal.

solution or 200 cc. of whole blood, the condition improved temporarily. In several instances the dog regained from 0.5 to 1 Kg. in weight.

The situation of the ulcers and the ease with which they could be approached made them particularly adaptable to the application of various types of treatment. Sodium bicarbonate was introduced into the pouch by means of a syringe and also given by mouth with the test meal. In either case it had the effect of depressing the acidity for from two to four hours, after which time the acidity returned to its former level and remained elevated for from fourteen to sixteen hours (fig. 4). Mucin introduced into the pouch in doses of 8 Gm. twice daily stimulated the secretion of acid and did not prevent the formation of an

ulcer. However, these experiments were made before the investigations of Rivers, Vanzant and Essex [3] had been carried out, so it is possible that an impure product was used. The ulcer that formed in the presence of mucin was of a type different from the others; it was much larger, but it did not have the same tendency to perforate, and bleeding did not occur.

A method of treatment which was suggested by Mann and Bollman [4] was successful in preventing the formation of ulcers and also in healing them. The preparation used consisted of: gelatin, 100 Gm.; acacia, 150 Gm.; water, 500 cc., and olive oil, 300 cc. The gelatin, acacia and water were heated together over a water bath until dissolved. The lecithin was dissolved in some of the olive oil over an open flame, and

Fig. 5.—Healing of an ulcer subsequent to three weeks' treatment with the emulsion. Note the small bud of granulation tissue in the center.

the oil was then mixed into the gelatin, acacia and water so that a thick emulsion resulted. In treating an ulcer, the mixture was heated until it would flow, and from 20 to 30 cc. was inserted into the pouch twice daily by means of a syringe. The emulsion was markedly tenacious and did not stimulate the secretion of acid. It left the stomach intact in about six hours.

Five dogs were treated with this emulsion. In one of the dogs the treatment was started immediately following the second stage of the

3. Rivers, A. B.; Vanzant, F. R., and Essex, H. E.: The Dangers of Using Impure Mucin in the Treatment of Peptic Ulcer, J. A. M. A. **98**:1156 (April 2) 1932.

4. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers: Development and Treatment, J. A. M. A. **99**:1576 (Nov. 5) 1932.

operation, and an ulcer did not develop. In the others, treatment was not started until there was definite evidence of the formation of an ulcer, such as bleeding, loss of weight and so forth. In the dogs in which an ulcer had already formed, healing of the ulcer was effected in about three weeks by continuous treatment, and healing was accompanied by an apparent decrease in the acidity of the secretion from the pouch and also by an increase in the appetite and in the weight of the animal.

Pathologic changes in this healing process were the same as in the healing process described by Mann.[5] In early stages the defect was

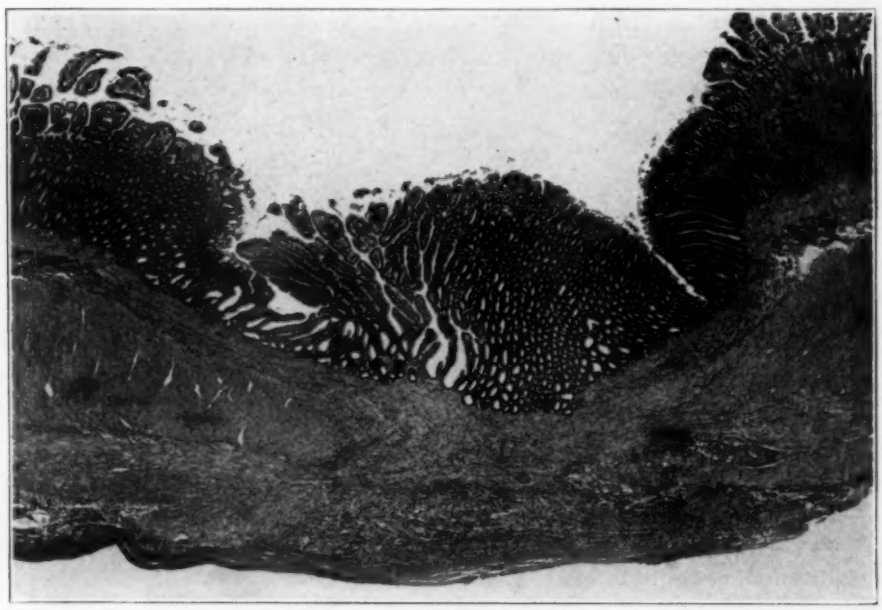

Fig. 6.—Section of a healed ulcer which had been treated with the emulsion. Note the atypical mucosa and the defect in the muscularis, the two most important histologic characteristics of a healed ulcer.

filled in with a bud of granulation tissue, and a single layer of mucosal cells grew over this bud. As the healing process continued, the bud of granulation tissue was pinched off and the area became covered with newly formed mucosa which finally developed into typical intestinal villi. The layers of muscle which were destroyed did not regenerate, but the defect was filled in by fibrous scar tissue which remained as evidence of the previously existing ulcer (figs. 5 and 6).

5. Mann, F. C.: Production and Healing of Peptic Ulcers: An Experimental Study, Minnesota Med. **8**:638 (Oct.) 1925.

COMMENT

A method has been described by which a type of chronic peptic ulcer can be produced experimentally with great uniformity. The method consists in making a pouch of fundic mucosa and draining it with a loop of intestine. The ulcer develops in the intestinal loop just distal to the stoma of the pouch. These ulcers differed from peptic ulcers found in man in that they were entirely separate from the main gastro-intestinal tract; their isolation from the main gastro-intestinal tract made them readily accessible, facilitated the study of their development and showed the effect of different methods of treatment.

A number of factors have been considered by various workers as significant in the etiology of peptic ulcer. Many of these factors can be eliminated in regard to this type of ulcer. In the first place, a faulty supply of blood did not play a part, as shown by the fact that an ulcer never developed after the first stage when the intestinal loop was isolated and anastomosed to the stomach, although by this operation the supply of blood to the fistula was impaired. During the second operation, in which the pouch was made, the supply of blood to the fistula was not affected in any way. In the second place, operative and external traumas were not factors of importance in producing these ulcers, because an ulcer did not develop even when a catheter was passed repeatedly following the making of the fistula. It is not likely that infection was a factor in the development of these ulcers, although, the part played by infection is difficult to evaluate. That faulty suture material was not of etiologic significance is indicated by the fact that the ulcers started not at the line of suture but about 1 cm. from it.

Mann and Williamson[6] and also Morton,[7] McCann,[8] Ivy and Fauley[9] and, more recently, Matthews and Dragstedt[10] have referred to three factors as significant in the development of peptic ulcer: the chemical factor, the mechanical factor and the susceptibility of the mucosa; all of these seemed to be of significance in the production of the experimental ulcers described. In these experiments the chemical

6. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409 (April) 1923.

7. Morton, C. B.: Observations on Peptic Ulcer, Ann. Surg. **87**:401 (March) 1928.

8. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

9. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, Am. J. Surg. **11**:531 (March) 1931.

10. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265 (Sept.) 1932. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. **8**:791 (May) 1924.

factor was demonstrated clearly. Other conditions being constant, an ulcer would not develop in the absence of free acid. Thus, if the cardiac or the pyloric portion of the stomach was used in making the pouch, no free acid was secreted and no ulcer developed. Likewise, if the intestinal mucosa was protected from the acid secretion by the use of a Pezzer catheter, an ulcer did not develop.

The mechanical factors which contribute to the formation of ulcers are difficult to evaluate. However, it seemed significant that in these animals the experimental ulcer developed uniformly at a point at which the secretion, emerging from the pouch into the fistula, met the obstruction in the fistula which prevented free drainage and thus caused a welling up of secretion in the first part of the fistula. It is also significant that in pouches drained by two fistulas an ulcer did not develop until one of the fistulous loops was removed. It may be that mechanical forces are important when gastric secretion is kept constantly in contact with exposed mucosa.

The third factor, mucosal susceptibility, which has also been emphasized by Matthews and Dragstedt,[10] was clearly brought out by the greater rapidity with which the ulcers formed when lower levels of the intestinal tract were used in making the fistulas. This illustrates a point that should be of significance in the etiology of gastrojejunal ulcers, namely, that the vulnerability of the mucosa to the development of ulcers increases as the distance from the pylorus becomes greater.

Although the ulcer was not situated in the main part of the gastrointestinal tract and did not come in contact with ingested food, a progressive and marked loss of weight occurred in each dog in which ulcer developed. This loss of weight was associated with loss of appetite, vomiting, dehydration and reduction of chlorides in the blood. A temporary gain in weight could be brought about by intravenous injections of saline solution or by transfusions. While carefully controlled experiments were not carried out to prove the point, it is possible that the loss of weight and other symptoms observed were due to a disturbance in the chemistry of the blood resulting from a loss of chlorides.

The method used in treating the ulcers was based on the hypothesis that substances which would coat the surface of the ulcer and protect it from the gastric secretion would promote healing under this coating. The preparation used was an emulsion of gelatin, acacia, olive oil and lecithin. The gelatin was used to hold the mixture together and make it more tenacious. The acacia supplied the adherent or protective qualities. The vegetable oil was used for three purposes: first, for its depressing effect on gastric secretion, as illustrated by the work of Pavlov[11] and others; second, because it leaves the stomach very slowly, as shown by

11. Pavlov, I. P.: The Work of the Digestive Glands, ed. 2, London, C. Griffin & Company, 1910.

Gianturco,[12] and third, because it has a protective action. The lecithin was used to make the emulsion smoother and also for its protective effect. The method described was successful in treating this type of ulcer in five experiments. Ulcers developed in all of the untreated animals, whereas in the five dogs that were treated with the emulsion, ulcers did not develop.

The fact that healing and destruction occur simultaneously in peptic ulcers is known. The purpose of using the method described was to protect the surface of the ulcer from the gastric secretion for a sufficient time to permit the healing process to go on to completion. Although there were not enough experiments carried out to prove the actual value of the method, the experiments did suffice to bring out the fact that an ulcer will heal in about three weeks if its surface is afforded sufficient protection. Neither sodium bicarbonate nor the preparation of mucin used was effective in preventing or healing these ulcers.

Pathologically, the specimens presented all of the characteristics typical of the various stages of the healing process as described by Mann for experimental ulcers and by Caylor [13] for ulcers of man.

SUMMARY

A method has been described for producing an experimental peptic ulcer in a loop of intestine forming a fistula from an isolated gastric pouch to the abdominal wall. An ulcer formed in each of the dogs in which the fundus of the stomach was used in making the pouch. Several facts were brought out in these experiments. It was shown that a combination of three factors was responsible for the development of these ulcers: the chemical factor, the mechanical factor and the factor of mucosal susceptibility. The chemical action of the gastric secretion was found to be of prime importance. The increasing vulnerability of the intestinal mucosa to the formation of ulcer as the distance from the stomach increased was demonstrated. The mechanical factor probably played a part, for the ulcer developed at a point where the gastric secretion was held constantly in contact with the exposed intestinal mucosa. It was found that an ulcer in an isolated gastric

12. Gianturco, Cesare: Some Mechanical Factors of Gastric Physiology: Study I. The Empty Stomach and Its Various Ways of Filling. The Pressure Exerted by the Gastric Walls on the Gastric Content. The Physical Changes Occurring to the Foodstuff during Digestion, Am. J. Roentgenol. **31**:735 (June) 1934; Some Mechanical Factors of Gastric Physiology: Study II. The Pyloric Mechanism. The Effect of Various Foods on the Emptying of the Stomach, ibid. **31**:745 (June) 1934.

13. Caylor, H. D.: The Healing of Gastric Ulcer in Man, Ann. Surg. **83**:350 (March) 1926.

pouch has the same effect in causing loss of appetite, vomiting and loss of weight as does an ulcer in the main gastro-intestinal tract.

A preparation consisting of an emulsion of gelatin, acacia, olive oil and lecithin, introduced into the pouch twice daily, was effective in the healing of these experimental ulcers and prevented their formation. The pathologic changes that occurred in the healing of the ulcers were found to be similar to the changes which occur in peptic ulcers in man. The method of treatment was considered important because it brought out the fact that an ulcer will heal in about three weeks if its surface is adequately protected from the gastric secretion. The emulsion used in treating the ulcers has been considered only from the experimental point of view, and no conclusion can be drawn regarding its possible clinical application.

LYMPHOSARCOMA

A CLINICAL, PATHOLOGIC AND RADIOTHERAPEUTIC STUDY, WITH A REPORT OF THIRTY CASES

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The purpose of this investigation was to correlate the clinical, roentgenologic and pathologic observations on a group of patients suffering from lymphosarcoma, with special emphasis on the differential diagnosis and the radiosensitivity of the associated mediastinal lesions.

In order to be of value a study of this type should fulfil several conditions: The clinical observations must be controlled by pathologic data; the ultimate fate of the patient must be known, and in case of death there must be a control by autopsy. All these conditions are fulfilled in this investigation.

The material on which this analysis is based consists of 30 cases of microscopically proved lymphosarcoma. The end-result is known in every case, constituting 100 per cent follow-up, and an autopsy was performed on each of the 13 patients who died in the hospital.

One of the most interesting and largely unexplained features of neoplastic diseases is the marked variations that are noted in the rate of progress and extension. This renders it highly important that we become familiar with the natural history of the different types of tumor and with their behavior under various therapeutic methods. Because of this circumstance, extensive clinical and pathologic material offers the opportunity to study extreme variations in the disease which more limited material usually fails to disclose.

AGE INCIDENCE

The patients in the Veterans' Administration Facility do not represent a random sampling of the population, but constitute a rather selected group, discharge from military service being the primary criterion for admission. Because of this the age incidence is not necessarily a true picture of the general incidence of the disease, but in spite of this cir-

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From the Cancer Research Unit, Veterans' Administration Facility, Hines, Ill.

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cumstance the age of onset of symptoms is of some interest; figure 1 indicates the age distribution in this series. The minimum age at the onset of symptoms was 30 years and 4 months, the maximum age, 61 years and 3 months, and the mean age, 43.2 years.

PATHOLOGY

Kundrat [1] was the first to give a clear description of lymphosarcoma as a growth arising from a group of lymph nodes, or, more rarely, from a single node or from lymphoid tissues such as are encountered in the tonsils, the pharynx or the intestinal tract. The lesion, composed of a reticulum in which lymphoid cells abound, destroys the capsule of the

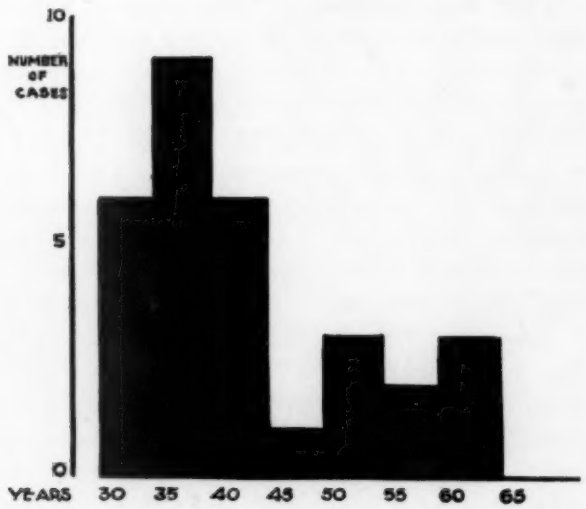

Fig. 1.—A chart showing the age at the onset of symptoms.

node and invades the adjacent lymph nodes. The separation of lymphosarcoma from the leukemias and pseudoleukemias was accomplished by Kundrat and Paltauf.

Metastatic tumors in distant organs are often observed. The disease tends, however, to grow through the lymph channels, with generalized involvement of groups of lymph nodes. The disease is sometimes limited to one region, such as the mediastinal lymph nodes, the retroperitoneal lymph nodes or the gastro-intestinal tract.

According to Ewing,[2] lymphosarcoma is to be distinguished from other forms of lymphoma by its local destructive capacity and by the

1. Kundrat: Ueber Lympho-Sarkomatosis, Wien. klin. Wchnschr. **6**:211, 1893.

2. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 1093.

formation of true metastases in different organs arising in a chain of lymph nodes. The tumors rapidly become bulky, infiltrate the surrounding tissue and tend to cause ulceration and necrosis of the skin and of the mucous membranes.

Histologically, lymphosarcoma is generally divided into two groups: (1) reticulum cell sarcoma or large round cell lymphosarcoma arising from the reticulum, and (2) malignant lymphocytoma arising from the lymphocytes. Ewing was of the opinion that in the great majority of cases the two varieties retain their separate identity and arise under different clinical conditions.

OBSERVATIONS AT AUTOPSY

Table 1 indicates the pathologic observations on 13 patients with lymphosarcoma who were examined at autopsy, showing various tissues and organs which were involved.

TABLE 1.—*Involvement of Tissues and Organs Observed at Autopsy*

	No. of Cases		No. of Cases
Skin and subcutaneous tissues	4	Liver	9
Cervical lymph nodes	7	Spleen	2
Axillary lymph nodes	6	Pancreas	6
Inguinal lymph nodes	5	Kidney	6
Peribronchial lymph nodes	9	Thymus	3
Retroperitoneal lymph nodes	8	Stomach	1
Mesenteric lymph nodes	3	Diaphragm	1
Lungs	1	Peritoneum	3
Pleura	7	Wall of the chest	1
Pericardium	4	Pharynx	1
Heart	2	Accessory nasal sinuses	1

CLINICAL VARIETIES

A study of this group of cases indicates that the following division into various clinical groups can be established:

1. Lymphosarcoma with generalized adenopathy and no special localization.[3]

2. Lymphosarcoma associated with localization in the tonsil, the pharynx or the base of the tongue.

3. Lymphosarcoma associated with pronounced involvement of the retroperitoneal lymph nodes.

4. Lymphosarcoma, with localization in the rectum.

5. Lymphadenoma.

6. Lymphosarcoma probably arising in the thymus and other thymic tumors of uncertain histogenesis.

3. Nine cases of a total of 30 fall into this category. Aside from the autopsy observations included in table 1 there are no points of special interest in the group.

LYMPHOSARCOMA WITH LOCALIZATION IN THE TONSIL, THE PHARYNX OR THE BASE OF THE TONGUE

In the cases of 100 patients with nasopharyngeal tumors treated at the Memorial Hospital, New York, Ewing [4] reported the following pathologic diagnoses: transitional cell carcinoma, 47 cases; squamous cell carcinoma, 30; lymphosarcoma, 15; lympho-epithelioma, 11; adenoid-cystic epithelioma, 4, and malignant adenoma, 3. Thus, lymphosarcomas constituted 15 per cent of the group of nasopharyngeal tumors. The relative frequency of lymphosarcoma associated with lesions of the tonsils, the pharynx and the cervical lymphatic glands has suggested to some that an infectious agent is the etiologic factor (Chiari).

CASE 1.—A. W. was a man aged 70, in whom the first sign of disease was enlargement of the right submaxillary lymphatic glands. The lesions were removed and were proved histologically to be reticulum cell lymphosarcoma. One year later there developed an abdominal tumor, and at an exploratory operation a large retroperitoneal mass attached to the right kidney was discovered and removed with the kidney. The histologic structure was similar to that found in the submaxillary lymphatic glands. Six months later, or eighteen months after the first sign of disease, an ulcerative lesion 2 by 2 cm. was noted on the right side of the base of the tongue. A biopsy on this lesion showed lymphosarcoma, the structure being similar to that discovered in the submaxillary glands and the retroperitoneal mass. Radium treatment over the mass in the tongue resulted in its complete disappearance. At the time of writing there is no further clinical evidence of the disease.

Lymphosarcoma associated with lesions of the tonsil may be unilateral or bilateral. It frequently grows to large dimensions and is seen as a bulky tumor which does not ulcerate until late. The cervical lymphatic glands are almost always involved in the early stage of the disease. In rare cases the disease is localized to the tonsil and the regional lymphatic glands, and adequate irradiation results in the disappearance of the lesion, the patient sometimes remaining well for prolonged periods. Minot and Isaacs [5] reported 1 patient well after six years. Others have reported long survivals. In most instances the disease in the tonsil or nasopharynx and the associated cervical lymphatic glands constitutes only a local expression of generalized lymphosarcomatosis, as exemplified in the 5 cases to be reported. Clinically and histologically lymphosarcoma of the tonsil and nasopharynx can be easily confused with lympho-epithelioma and transitional cell carcinoma, all three lesions being highly, and equally, radiosensitive. In many cases the similarity is so striking that a differential diagnosis is exceedingly difficult.

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4. Ewing, J.: Radiosensitivity, Radiology **13**:313 (Oct.) 1929.

5. Minot, G. R., and Isaacs, R.: Lymphoblastoma: Aspects Concerning Abdominal Lesions Especially Their Production of Early Symptoms, Am. J. M. Sc. **172**:157 (Aug.) 1926; Lymphoblastoma (Malignant Lymphoma): Age and Sex Incidence, Duration of Disease, and Effect of Roentgen Ray and Radium Irradiation and Surgery, J. A. M. A. **86**:1185 (April 17); 1265 (April 24) 1926.

CASE 2.—A. K., a man aged 40, had generalized adenopathy which was first noted in the left cervical region in January 1932. Dyspnea and loss of weight developed four months later. A biopsy on a node showed lymphosarcoma. Physical examination revealed generalized enlargement of the lymph nodes, and roentgenologic examination showed a widening of the mediastinal shadow. There was marked edema of the lower extremities. There were numerous cutaneous and subcutaneous, firm, movable nodules in the scalp. In the left tonsillar fossa was a mass pushing the anterior tonsillar pillar forward and extending downward toward the epiglottis. The lesion failed to respond to irradiation. The patient's general condition grew rapidly worse, and he died soon after admission. At autopsy it was found that the entire lymphatic system was involved. All the lymph nodes were invaded, and there were metastases in the spleen, the liver and the kidneys.

Fig. 2 (case 4).—*A* shows large masses in the supraclavicular and cervical areas before treatment. There was also a nasopharyngeal growth. *B* shows the same areas after treatment. The disease recurred promptly, and the patient died two months later.

CASE 3.—F. K., a man aged 43, was admitted to the hospital on May 13, 1932, with a history that three months previously he first noted soreness of the throat and difficulty in swallowing, followed by the appearance of a mass in the left cervical region. Examination revealed a mass in the posterior nasopharynx, with metastasis to the right cervical lymph nodes. Microscopic examination of a biopsy specimen revealed reticulum cell lymphosarcoma. External irradiation resulted in a moderate regression of the primary and metastatic lesions. In July 1932, the patient was readmitted to the hospital with recurrence and extension to the left middle ear, resulting in deafness. External irradiation with the radium "bomb" resulted in marked improvement of the local lesion and in disappearance of the pain and deafness. The patient was readmitted in October 1932, with renewed activity of the primary lesion, paralysis on the right side of the face, extreme weakness and dyspnea. The patient died eleven days later of terminal

bronchopneumonia. Autopsy revealed that the nasopharyngeal lesion had extended to all the accessory sinuses. No visceral metastases were found. Microscopically the lesion was a reticulum cell lymphosarcoma.

CASE 4.—J. Y., a man aged 61, first noticed a small gland in the right submaxillary region in November 1932, followed by rapid enlargement of the cervical glands on both sides. About the same time the patient became aware of a growth in the left nostril which interfered with his breathing. Examination revealed a large mass in the posterior nasopharynx and extensive bilateral submaxillary, cervical, supraclavicular, axillary and inguinal adenopathy (figs. 2 and 3). A biopsy specimen from the nasopharyngeal mass showed reticulum cell lymphosarcoma (fig. 4).

Roentgen therapy resulted in rapid regression and the disappearance of the nasopharyngeal growth and the cervical adenopathy. The patient was able to breathe easily, his general condition improved markedly, and he gained 10 pounds (4.5 Kg.). One month later the right axillary and right infraclavicular masses

Fig. 3 (case 4).—*A* shows masses in the infraclavicular and axillary areas before treatment; *B* shows the same areas after treatment.

recurred, and a second cycle of radiation was administered with moderate regression. One month later the disease recurred and became widely disseminated, and the patient died at home. Autopsy was not performed.

CASE 5.—L. F., a man aged 32, was first admitted to the hospital April 6, 1932. Two and one-half years previously a growth was removed from the nose, which recurred three months later. There was moderate obstruction to breathing but no pain. Examination revealed the right nares to be filled with a bulky, soft tumor. There was swelling of the right nares, with bulging of the lateral wall. The growth extended through the soft palate, filled the nasopharynx and involved the right antrum (fig. 5). There was extensive cervical adenopathy. Examination of the biopsy specimen revealed lymphosarcoma (fig. 6). External irradiation resulted in a marked reduction in the size of the tumor. Six months later the patient was readmitted to the hospital with a swelling over the right antrum and a recurrence of the tumor in the nasopharynx. External irradiation resulted in marked regression. The patient was readmitted in March 1933 with exophthalmos

of the right eyeball, recurrence in the nasopharynx and cervical adenopathy on the right side. At the time of writing the patient is totally blind.

CASE 6.—J. B., a man aged 38, had a swelling on the left side of the neck which first appeared in January 1931. There was a rapid increase in the size of the mass, accompanied by severe pain. Examination in May 1931 revealed enlargement and ulceration of the left tonsil. The tonsil was removed, and a microscopic diagnosis of chronic inflammation was made. In October 1931, enlargement of the

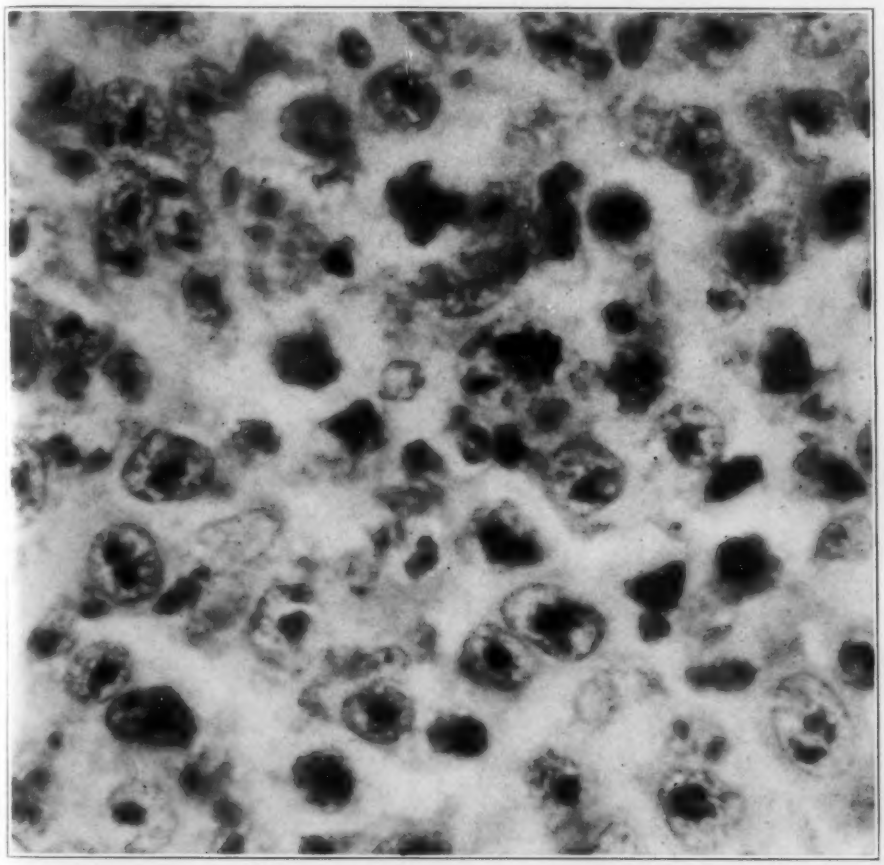

Fig. 4 (case 4).—A photomicrograph of a section of a reticulum cell lymphosarcoma of the nasopharynx.

cervical nodes on the left side was noted. Microscopic examination of a biopsy specimen showed lymphosarcoma. External irradiation was administered. In January 1933 there was further evidence of recurrence in the cervical nodes, and the patient died in February.

Comment.—Case 1 is an example of generalized lymphosarcomatous disease in which the base of the tongue was one of the foci. The slow progress of the disease is noteworthy. Case 2 is an example of wide-

spread lymphosarcomatosis in which the tonsil was one of the numerous foci. Case 4 is another example of widespread disease in which a nasopharyngeal growth was present. The marked and rapid response to irradiation (figs. 2, 3 and 4) in the presence of widespread disease points to a bad ultimate prognosis. The rapid response to irradiation indicates a high degree of malignancy as well as marked radiosensitivity. In the other 3 cases the disease was more localized. Cases 3 and 5 illustrate the extension of the disease upward toward the accessory sinuses, with involvement of the cranial nerves. In case 3 the disease finally extended to the brain, causing paralysis of the facial nerve. In case 5 the disease extended upward, invaded the accessory nasal sinuses and ultimately caused total blindness. In spite of the wide local extent of the disease neither patient showed evidence of visceral metastases. In case 3 the absence of metastasis was proved at autopsy. The upward

Fig. 5 (case 5).—A photograph showing perforation of the palate by a lymphosarcoma of the nasopharynx. The disease extended upward, causing total blindness.

extension of the disease is characteristic of lympho-epithelioma of the nasopharynx and accessory nasal sinuses. In these cases, evidence of involvement of the cranial nerves was also discovered with considerable frequency.

LYMPHOSARCOMA LIMITED TO THE RETROPERITONEAL LYMPH NODES

In some examples the lymphosarcomatous process is limited to the retroperitoneal lymph nodes. In these cases the presence of a retroperitoneal mass gives rise to a characteristic clinical entity. In other examples the retroperitoneal mass, while dominating the clinical picture, is associated with the disease in the other lymph nodes. Pressure on and involvement of the gastro-intestinal tract are not uncommon. In these cases the symptoms are essentially gastro-intestinal. The retroperitoneal

mass is highly radiosensitive, and startling primary regressions are usually noted after radiotherapy. However, the disease has a tendency to recur and to become widely disseminated. Following radiotherapy the patient may be clinically free from the disease for prolonged periods.

Minot and Isaacs [8] reported that 25 per cent of 477 patients with lymphoblastoma (exclusive of lymphatic leukemia) had as their initial symptom one referable to an abdominal lesion. Twenty per cent of a

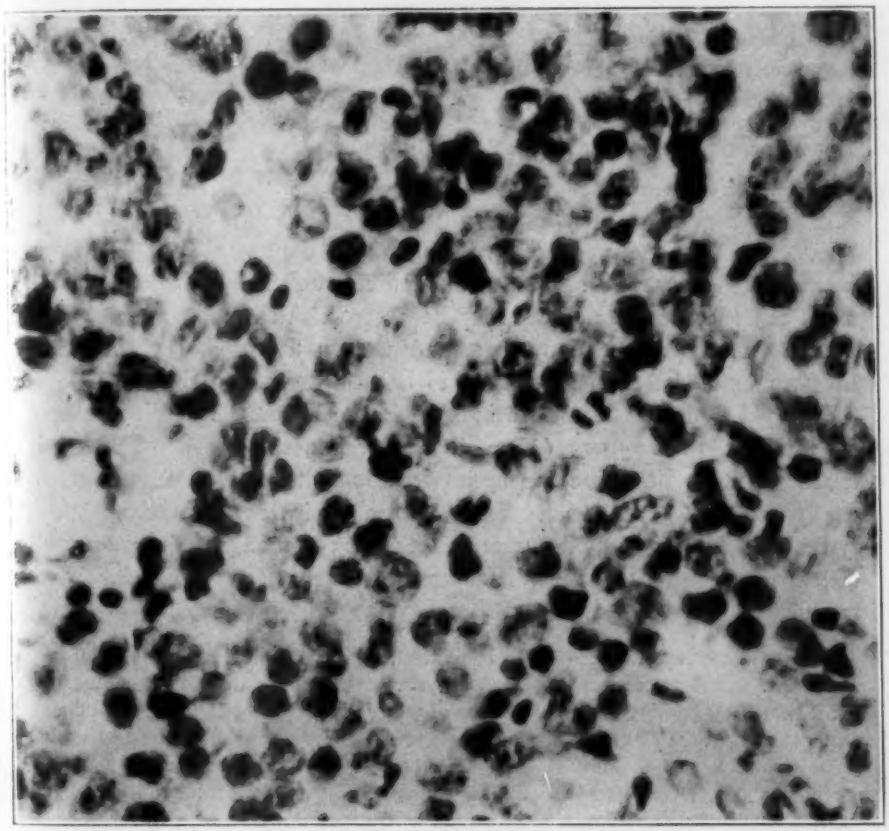

Fig. 6 (case 5).—A photomicrograph of a reticulum cell lymphosarcoma which began in the right nasopharynx and extended upward to the accessory nasal sinuses.

second group of 71 deceased patients without such initial symptoms had abdominal symptoms early in the course of their illness. Late in the disease abdominal symptoms occurred with great frequency. The pain, which was often intense, occurred in the abdomen and back or in the legs.

A résumé of the observations at autopsy (table 1) indicates that the retroperitoneal lymph nodes were involved in 8 of 13 cases. In this

series there was only 1 example in which the disease was localized in the retroperitoneal lymph nodes.

CASE 7.—J. M., a man aged 41, about August 1929 began to have vague abdominal distress accompanied by vomiting. Soon he suffered from fatigue on exertion, and there was gradual loss of weight. These symptoms continued for over two years before he was admitted to the hospital on Aug. 10, 1931. On examination a large, firm, fixed mass was discovered in the lower left quadrant of the abdomen. Evidence of nephritis and uremia soon developed, and the patient died. At autopsy it was found that the upper part of the left kidney and suprarenal gland were enveloped in a firm, white mass extending to and including the pancreas, which it bound firmly to the spine. The growth extended to the iliopsoas muscle and surrounded, but did not invade, the great vessels. The anatomic diagnosis was retroperitoneal lymphosarcoma invading one kidney and the pancreas. Histologically the tumor was a small cell lymphosarcoma.

LYMPHOSARCOMA ASSOCIATED WITH LESIONS OF THE RECTUM

Lymphosarcoma may affect any portion of the gastro-intestinal tract, including the appendix. The microscopic structure is that of either a small cell or a large round cell lymphosarcoma. In 1929 Bensaude, Cain and Horowitz [6] reported 3 cases, and after a thorough review of the literature stated that the subject had been so neglected that until 1929 they could find only 12 authentic cases in the literature. These authors distinguished two types: (1) a diffuse or generalized form, which is characterized by its structure, by its development and by its extension to the lymph nodes and (2) a localized form, which sometimes shows the typical structure of lymphosarcoma but most commonly resembles round cell sarcoma so closely that differentiation is extremely difficult. They reported 3 examples of the diffuse form.

One patient, aged 65, first had cervical, axillary and inguinal adenopathy which responded to radiotherapy. Five years later marked enlargement of one tonsil was noted; nine years after the onset of the disease a filling defect was demonstrated in the sigmoid flexure and on proctoscopic examination a nonulcerated mass was discovered, situated 12 cm. from the external anal orifice. Biopsy revealed a small cell lymphosarcoma. Roentgen therapy was administered, but the general condition of the patient became worse, and an ileostomy was performed because of obstruction. He died several months later of progressive cachexia.

The second patient was a woman, aged 74, in whom in 1924 there developed adenopathy in the left supraclavicular region. The nodes were removed one year later (1925), and a microscopic diagnosis of malignant lymphoma was made. In 1927 the patient was admitted with generalized adenopathy, abdominal masses and an enlarged spleen, all of which disappeared under radiation therapy. Rectal pain and constipation first appeared in October 1926. Rectal examination in March 1927 revealed a bulky, nonulcerated mass 4 cm. from the external anal orifice. A biopsy specimen showed lymphosarcoma. Radiotherapy resulted in the complete disappearance of the rectal growth, but the patient was lost sight of, and the ultimate result is not known.

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6. Bensaude, R.; Cain, A., and Horowitz: Le lymphosarcome du rectum, Ann. de méd. **26**:405 (Dec.) 1929.

The third patient was a woman, aged 67, in whom, in December 1928, there first developed bilateral cervical and preauricular adenopathy followed by severe intractable diarrhea. Examination revealed extensive adenopathy on the left cervical and supraclavicular side. Proctoscopic examination revealed a large, nonulcerated mass about 12 cm. high, which on microscopic examination proved to be a reticulum cell lymphosarcoma. The patient died. Autopsy revealed involvement of the peribronchial, retroperitoneal and mesenteric nodes. The rectum showed diffuse involvement in the lymphosarcomatous process.

Bensaude, Cain and Horowitz [6] cited 9 cases (reported by other authors) of localized lymphosarcoma of the rectum. Noel Lapeyre's [7] patient was a woman, aged 28, in whom there developed a bulky tumor above the sphincter of the rectum. Rectal amputation was performed. Microscopically there were hypertrophied lymph follicles which could be traced to the fully developed neoplastic process. The patient reported on by Stolz, Gunsett and Oberling,[8] aged 66, had an ulcerated tumor which extended 5 cm. along the lower portion of the rectum without causing stenosis and was fixed to the sacrum posteriorly and to the vagina anteriorly. The tumor was regarded as inoperable. The treatment consisted of radium puncture by the vaginal and by the rectal routes supplemented by external irradiation. The tumor disappeared, and the patient had remained well for over six years when the report was made. Hessert's [9] patient was 50 years of age. The growth was resected, and the patient was free from disease seven months later. In his original contribution Kundrat [1] mentioned 1 case of inoperable tumor of the rectum which was diagnosed clinically as cancer, but which at autopsy proved to be lymphosarcoma. Key's [10] patient was 41 years of age. A slowly growing, nonulcerated tumor of the rectum developed just above the sphincter. Partial removal of the mass was followed one month later by recurrence and extension of the disease. Exner's [11] patient, a man, aged 43, suffered from a circumscribed, ulcerated tumor of the midportion of the rectum. The rectum was removed, and microscopic examination of the growth revealed a small round cell lymphosarcoma. The patient was well two years later. A second patient of Exner presented a mushroom-like tumor which on resection proved to be a lym-

7. Lapeyre, N. C.: Primary Sarcoma of Rectum, Rev. de chir., Paris **58**:223 and 281, 1920.

8. Stolz, J.; Gunsett, A., and Oberling, C.: Lymphosarcome du rectum. Radio et Curiethérapie. Guérison depuis six ans, Bull. Assoc. franç. p. l'étude du cancer **17**:63 (Feb.) 1928.

9. Hessert, W.: Lymphosarcoma of Rectum, Ann. Surg. **36**:459 (July-Dec.) 1902.

10. Key, E.: Drei Fälle von Rektalsarkom, Nord. med. Ark. **51**:26, 1905; Zur Kasuistik des Rektalsarkoms, ibid. **8**:1, 1908.

11. Exner, A.: Ueber nichtmelanotische Sarkome des Mastdarms, Med. Klin. **4**:858, 1908.

phosarcoma. Brachmann's patient was 15 years of age. A rectal tumor the size of a cherry proved on section to be a small round cell sarcoma, probably lymphosarcoma.

CASE 8.—F. S., a man aged 41, had suffered from diarrhea and rectal discomfort for two years. On rectal and proctoscopic examination a nodular growth 3 cm. in diameter was discovered on the anterior wall of the rectum 4 cm. above the anal sphincter. The tumor was not ulcerated and was firmly attached to the underlying structures. A wide surgical excision of the growth was performed, followed by irradiation with high voltage roentgen rays. Microscopic examination of the specimen revealed lymphosarcoma. The operation was performed in June 1931. The patient is free from the disease at the time of writing, three years later.

CASE 9.—H. H., aged 48, complained of pain in the lower portion of the abdomen of six months' duration but had no other symptoms. On examination there was a growth the size of a lime just above the anal sphincter. A biopsy proved it to be lymphosarcoma. The treatment consisted of the implantation of removable platinum radium needles and external radiation with the 4 Gm. radium "bomb." The tumor disappeared promptly, and the patient has been free from the disease for fourteen months at the time of writing. At no time was there evidence of the disease in other parts of the body.

CASE 10.—H. F., 53 years of age, for six months had had symptoms consisting of intermittent diarrhea alternating with constipation and some bleeding. No pain had been experienced, and there had been no loss of weight Examination revealed a lymphosarcoma at the rectosigmoid junction. Radium therapy resulted in the complete disappearance of the growth. Six months later there developed generalized adenopathy with enlargement of the submaxillary, cervical, axillary and inguinal nodes. The lesions responded to external therapy with the radium bomb, and the patient is now clinically free from the disease at the time of writing, one year and a half after the onset of symptoms and thirteen months after beginning the treatment.

Comment.—In case 8 a patient with localized lymphosarcoma was free from the disease three years after wide surgical removal of the lesion followed by irradiation. The most common site of the lesion is just above the sphincter, although the growth may appear at the rectosigmoid junction or anywhere along the colon or ileum. The perirectal and pelvic tissues are rarely invaded. The lesion usually covers a large area, presenting an irregular surface of the mucous membrane, which is frequently not ulcerated. The nodules are firm and elastic, lacking the induration of cancer. The localized forms frequently occur as more or less bulky masses just above the anal sphincter and are sometimes attached to a pedicle.

Persistent diarrhea which refuses to submit to medication is the most important clinical sign. Frequently there are alternating constipation and diarrhea. The course of the disease varies markedly, depending chiefly on whether the lesion is isolated and localized, or is part of generalized lymphosarcomatosis.

Cure of localized lymphosarcoma of the rectum is recorded by wide surgical extirpation alone, by adequate radiotherapy alone and by the

combined methods. In general, because of the marked radiosensitivity of the lesions, radiotherapy constitutes the method of choice. In certain cases treatment by interstitial radiation is useful. External irradiation should be utilized in all cases either alone or in conjunction with radium puncture or surgical excision, depending on the size, location and radiosensitivity of the tumor.

LYMPHADENOMA (LYMPHOMA)

Chronic enlargement of the lymph nodes limited to a group of nodes and not becoming generalized have been described by LeCount [12] as being of common occurrence. Under the terms "simple lymphoma," "lymphadenoma" and "hyperplastic lymphadenitis," Ewing [2] has given the following description of the pathologic observations:

Appearing in the neck, axilla, groin and subcutaneous tissues and sometimes in other regions, these groups of enlarged nodes form solid tumor-like masses, with little or no tendency to central necrosis. After reaching a certain size they may remain stationary for months or years, producing only local symptoms. The prolonged benign course is characteristic (LeCount's case continued for fifteen years). The structure is characterized by diffuse overgrowth of typical small lymphocytes. The lymph follicles in the early stages are increased in size and in number and exhibit prominent germ centers. The pulp tissue is composed of closely packed lymphocytes. The structure resembles that found in leukemia and pseudoleukemia. It may be distinguished from the former by the blood test and from the latter by its local character. The differentiation from lymphosarcoma may be difficult. The distinction must be made by the usual clinical and microscopic criteria of malignancy. One case, observed by Ewing, persisted for eighteen years, eventually proving fatal, with rapid local growth and asphyxia.

CASE 11.—M. E., a man aged 61, first noted enlargement of the submental nodes three months before his first admission to the hospital on Feb. 6, 1931. Soon afterward he noticed enlargement of the cervical and inguinal nodes and pain in both legs. Examination revealed enlarged discrete nodes in the cervical, axillary and inguinal regions. Roentgen examination of the chest revealed a homogeneous shadow at the base of the left lung, a sharply defined shadow in the region of the great vessels and an increased density at the right hilus. Roentgen therapy was administered over the cervical, axillary and inguinal regions and over the lungs and mediastinum with pronounced and rapid response. Ten months later the patient was treated for enlargement of the submental and supraclavicular nodes. Twenty months after the second recurrence he was readmitted with dyspnea, cough, expectoration, edema of the extremities and pain in the back. Examination revealed generalized adenopathy, ascites and myocardial disease. Irradiation again resulted in marked regression of the nodes and improvement in

12. LeCount, E. R.: Lymphoma: A Benign Tumor Representing a Lymph Gland in Structure, J. Exper. Med. 4:559, 1899.

the patient's general condition. The microscopic examination of a lymph node removed for biopsy revealed a structure characteristic of lymphadenoma (fig. 7). The patient is alive at the time of writing, three and one-half years after the onset of symptoms. The roentgen observations on the mediastinum taken three years apart are of interest (fig. 8).

Case 12.—R. V., a white man aged 43, first noted a mass in the left inguinal region in March 1928. In February 1931 a small tumor was removed from the

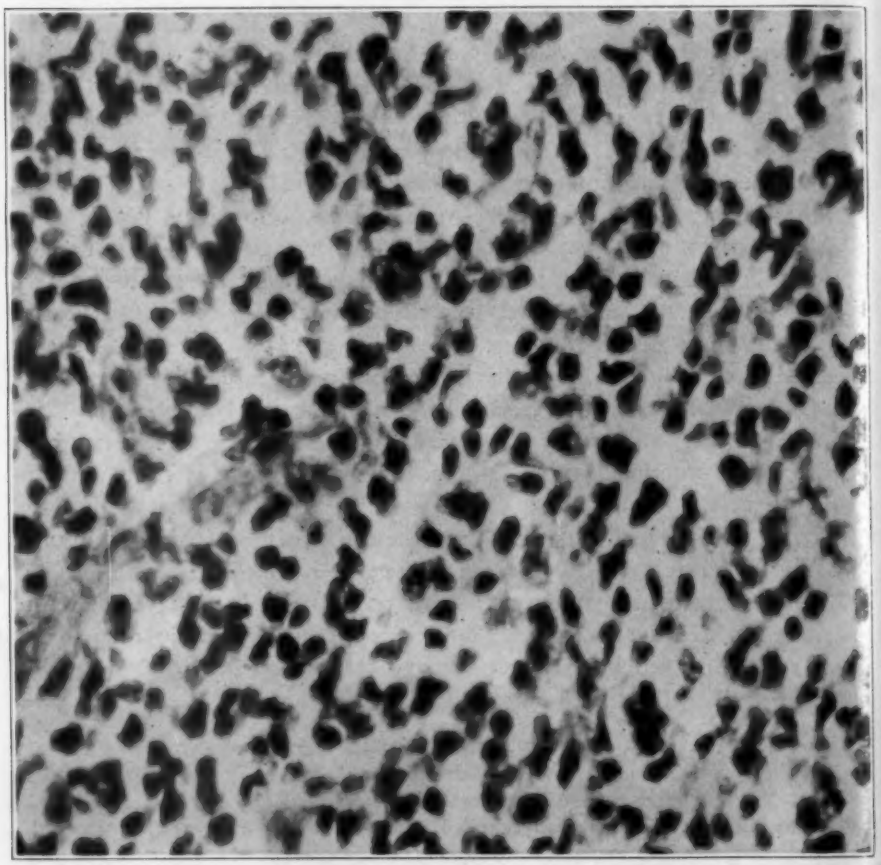

Fig. 7 (case 11).—A photomicrograph showing the structure of a lymphoma, or lymphadenoma, with the complete loss of the architecture but absence of the characteristics of fully developed lymphosarcoma.

left groin. Three weeks later he was admitted to the hospital for postoperative irradiation. Microscopic examination of tissue removed at the operation revealed the characteristic features of lymphoma. There was a partial loss of the architecture, with the lymph follicles still recognizable. In the center of some of the follicles occasional mitotic figures were seen (fig. 9). External radiation was given over the operative site. In December 1932 enlarged nodes appeared in the right inguinal region and disappeared after external irradiation with roentgen rays. At

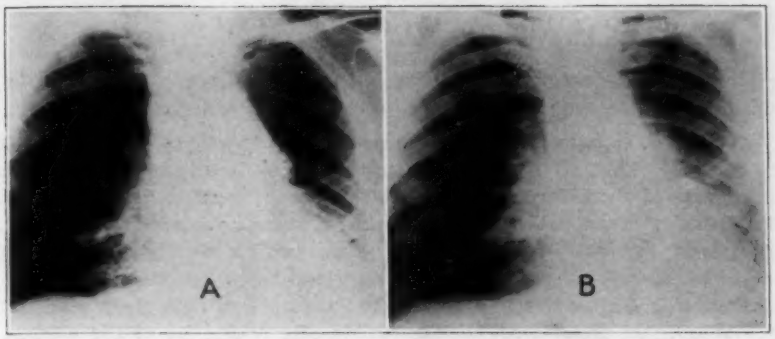

Fig. 8 (case 11).—Roentgenograms of the lungs. *A* shows a widening of the lower part of the mediastinum before treatment. The microscopic diagnosis was lymphadenoma. *B* shows the same area three years later at the time of a local recurrence of the disease.

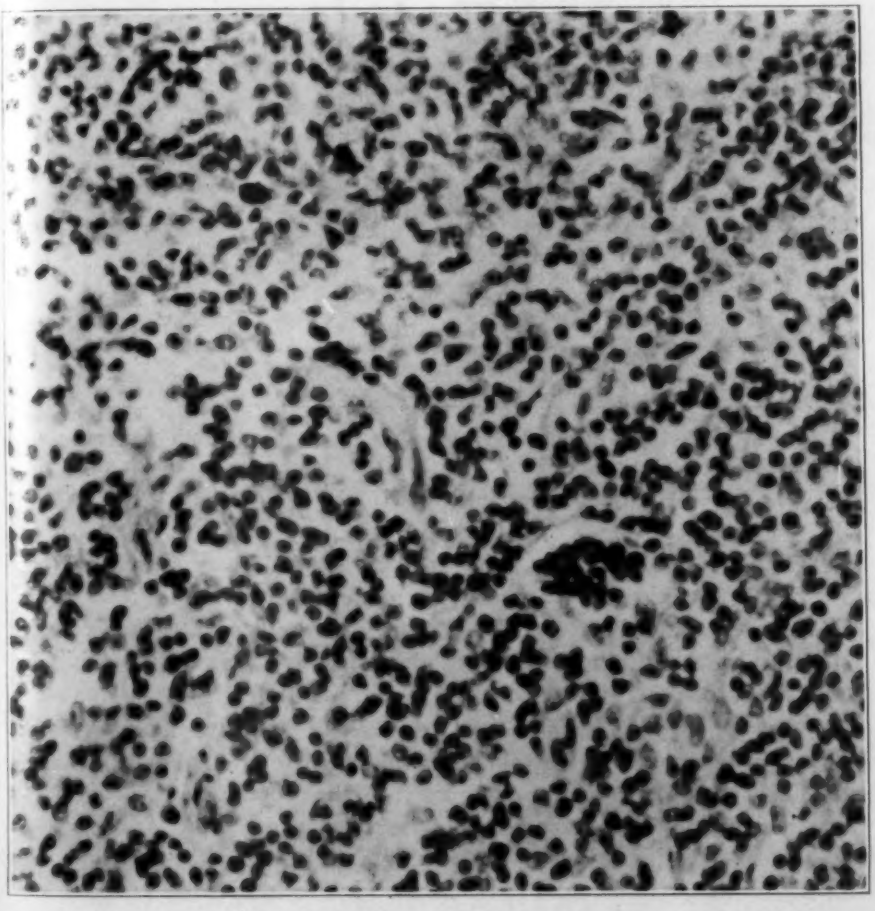

Fig. 9 (case 12).—A photomicrograph showing the structure of a lymphoma, or lymphadenoma. There is a partial loss of the architecture, but the cells are typical, with only occasional mitoses. The structure lacks the characteristics of fully developed lymphosarcoma.

the present writing the patient is alive but shows evidence of recurrence in the left inguinal region, with edema of the left leg. He is under treatment.

CASE 13.—J. G., a man aged 56, first noted a small swelling in the right side of the neck about 1930. It increased in size until it involved both sides of the neck. Soon afterward there developed dyspnea, fatigue on exertion, palpitation, vertigo and dysphagia. Examination revealed marked bilateral enlargement of the cervical, axillary and inguinal lymph nodes. The microscopic examination of a node removed for biopsy revealed a structure characteristic of lymphadenoma. In May 1933 external radiation was administered to all the lymph node areas with marked improvement. In December 1933 the patient was readmitted to the hospital on account of recurrence, and irradiation again resulted in a marked regression of the lesions. As in the preceding cases the adenopathic processes exhibited a high degree of radiosensitivity.

THYMIC TUMORS

The classification of thymic neoplasms has presented formidable difficulties, mainly because of the lack of knowledge concerning the

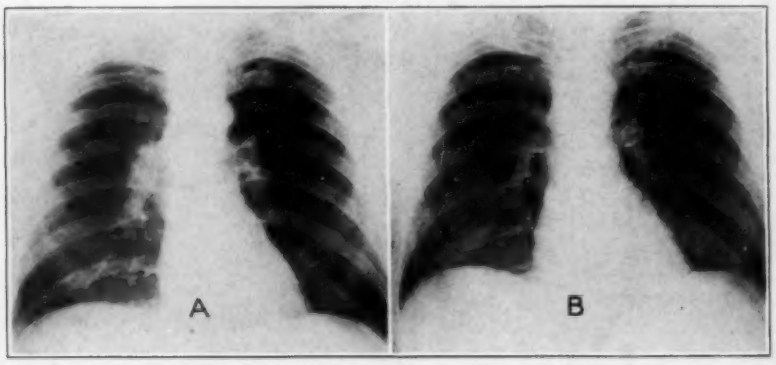

Fig. 10 (case 14).—Roentgenograms of the lungs. *A* shows a widened mediastinal shadow before roentgen therapy. The microscopic diagnosis was thymoma. *B* shows the same area eight months after treatment.

histogenesis of the thymic cells or the so-called thymic lymphocytes forming the reticulum and parenchyma of the thymus gland. This difficulty is intensified by the extreme variations in the histologic structure of these tumors, which render a histologic classification highly confusing and extremely uncertain.

According to Ewing[2] thymic tumors fall into two main groups: (1) lymphosarcoma or thymoma, composed of round, polyhedral and giant cells, and (2) carcinoma, arising from the reticulum cells. Lymphosarcoma is the more common of the two, and Ewing found little difficulty in distinguishing thymic tumors at autopsy from tumors of the mediastinal lymph nodes or the lungs. Thymic tumors have a tendency to surround and compress the trachea, bronchi, pericardium and great vessels. The bronchial, cervical and axillary nodes are frequently

involved. Extension and metastases to the following organs are of common occurrence: pleura, lungs, pericardium, spleen, liver, suprarenal glands, pancreas, kidneys and brain. Perforation of the sternum is not uncommon, and cases of metastases to bones have been recorded.

Histologically, some forms of thymoma resemble Hodgkin's disease, while others possess the characteristic features of lymphosarcoma. The thymic carcinomas are composed of pavement, cuboidal or cylindric epithelium. Mixed forms have been recorded by various observers.

Margolis [13] reviewed the literature on the histogenesis, pathology and the classification of thymic tumors and presented an excellent critical review of the subject. Two opposite views are held as to the histogenesis of the thymic cells. Some authors have held that the small thymic cells are related to the blood lymphocytes and that they are therefore of mesenchymal origin (Maximow,[14] Blum, Pinner [15] and Hammar [16]). Another group of workers advance the belief that the small thymic cells arise from the entodermal thymic reticulum (Nusbaum and Prymak,[17] Stöhr,[18] Bell,[19] Prenant, Dustin [20]). Margolis reported 6 cases of thymic tumor and arrived at the following conclusions:

> A rigid classification of tumors of the parenchyma is not possible at present because of the lack of definite knowledge concerning the histogenesis of all the elements of the thymic parenchyma, and because of the marked polymorphism of the cells which constitute most of such tumors. For this reason the designation

13. Margolis, H. M.: Tumors of Thymus: Pathology, Classification and Report of Cases, Am. J. Cancer (supp.) **15**:2106 (July) 1931.

14. Maximow, A.: Untersuchungen über Blut und Bindegewebe: II. Ueber die Histogenese der Thymus bei Säugetieren, Arch. f. mikr. Anat. **74**:525, 1909; IV. Ueber die Histogenese der Thymus bei Amphibien, ibid. **79**:569, 1912; V. Ueber die embryonale Entwicklung der Thymus bei Selachiern, ibid. **80**:39, 1912; A Textbook of Histology, completed and edited by W. Bloom, Philadelphia, W. B. Saunders Company, 1930.

15. Pinner, Max: Zur Frage der kleinen Thymusrindenzellen, Frankfurt. Ztschr. f. Path. **23**:479, 1920.

16. Hammar, J. A.: Zur Kenntnis der Teleostierthymus, Arch. f. mikr. Anat. **73**:1, 1908; Ueber Thymusgewicht und Thymuspersistenz beim Menschen, Anat. Anz. (supp.) **27**:121, 1905.

17. Nusbaum, J., and Prymak, T.: Zur Entwickelungsgeschichte der lymphoiden Elemente der Thymus bei den Knochenfischen, Anat. Anz. **19**:6, 1901.

18. Stöhr, P.: Ueber die Natur der Thymus-Elemente, Anat. Hefte **31**:407, 1906.

19. Bell, E. T.: Tumors of the Thymus, J. Nerv. & Ment. Dis. **45**:130 (Feb.) 1917.

20. Dustin, A. P.: Recherches d'histologie normale et expérimentale sur le thymus des amphibiens anoures, Arch. de biol., Paris **28**:1, 1913; A propos d'une thèse récente sur la biologie du thymus, Arch. de zool., expér. et gén. **55**:95, 1915-1916.

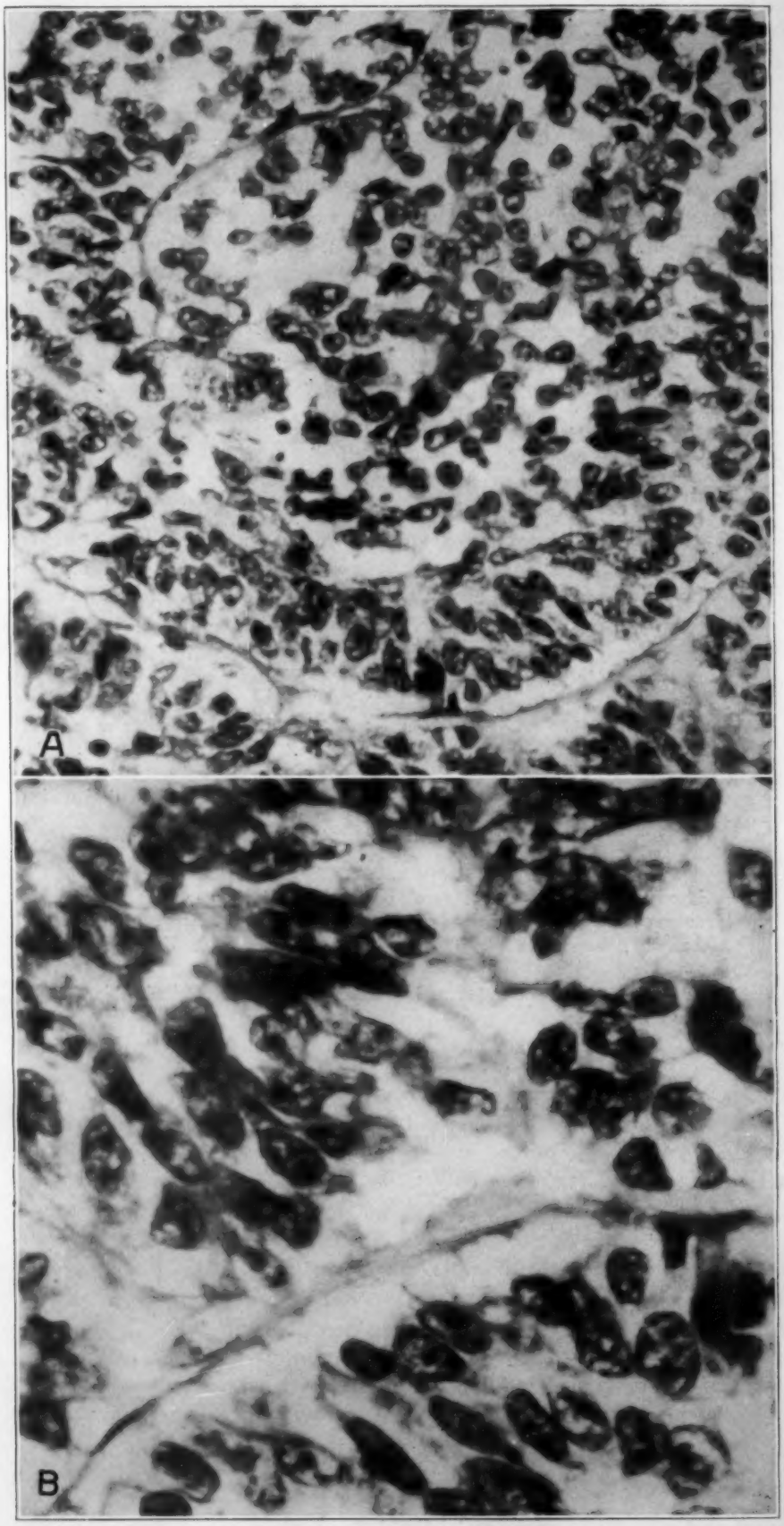

Fig. 11 (case 14).—*A*, a low power photomicrograph, shows a carcinoma of the thymus. *B* is a high power photomicrograph of the same section. The lesion proved to be moderately radiosensitive.

of thymoma for all tumors derived from the parenchyma of the organ seems more satisfactory than their classification as carcinomas and lymphosarcomas. Careful study of tumors of the thymus of the type often designated lymphosarcoma suggests that the sarcomatous appearance of the tissue may represent only a morphologic variation of a type of cell derived from the thymic reticulum. For the present the designation of sarcoma, including lymphosarcoma of the thymus, should be reserved for those tumors apparently derived from elements within the stroma of the thymus.

Crosby [21] collected 166 cases of malignant disease of the thymus gland. In 122 of these the growth was classified as sarcoma and in 44, as carcinoma. In a series of cases of mediastinal neoplasms Haagensen [22] reported 2 cases of carcinoma of the thymus with complete clinical and pathologic data, including observations at autopsy. He emphasized their radioresistance and called attention to the importance of this fact

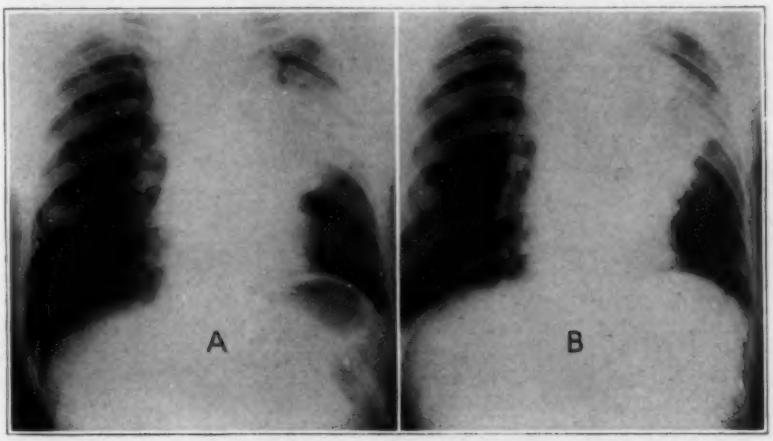

Fig. 12 (case 15).—Roentgenograms of the lungs. *A* shows an extensive mediastinal mass, probably originating in the thymus, before treatment; *B* shows the same area after treatment. The lesion proved to be radioresistant.

in relation to the differential diagnosis of primary mediastinal tumors. In 1932 Craver and MacComb [23] reported 3 cases of tumefaction of the thymus in association with lymphatic leukemia and reviewed the literature. The high radiosensitivity of the lesion was noted, and attention was directed to the importance of a careful investigation of the blood and of the lymph nodes when enlargement of the thymus is discovered.

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21. Crosby, E. H.: Malignant Tumors of Thymus Gland, Am. J. Cancer **16:** 461 (May) 1932.

22. Haagensen, C. D.: Differential Diagnosis of Primary Neoplasms of Mediastinum, Am. J. Cancer **16:**723 (July) 1932.

23. Craver, L. F., and MacComb, W. S.: Lymphatic Leukemia with Thymic Enlargement, Am. J. Cancer **16:**277 (March) 1932.

CASE 14.—W. C., a man aged 44, noted a painless swelling on the right side of the neck in May 1927. In January 1928 a biopsy on the cervical mass was reported to show lymphosarcoma. External radiation resulted in the complete disappearance of the mass. The patient remained well for five years, when a local recurrence was noted in the same area. Examination in March 1933 revealed a mass 15 by 6 cm. reaching from the right mastoid process to the angle of the jaw. There was no other adenopathy. Roentgen examination of the lungs revealed a mediastinal shadow (fig. 10 *A*). External irradiation with roentgen rays resulted

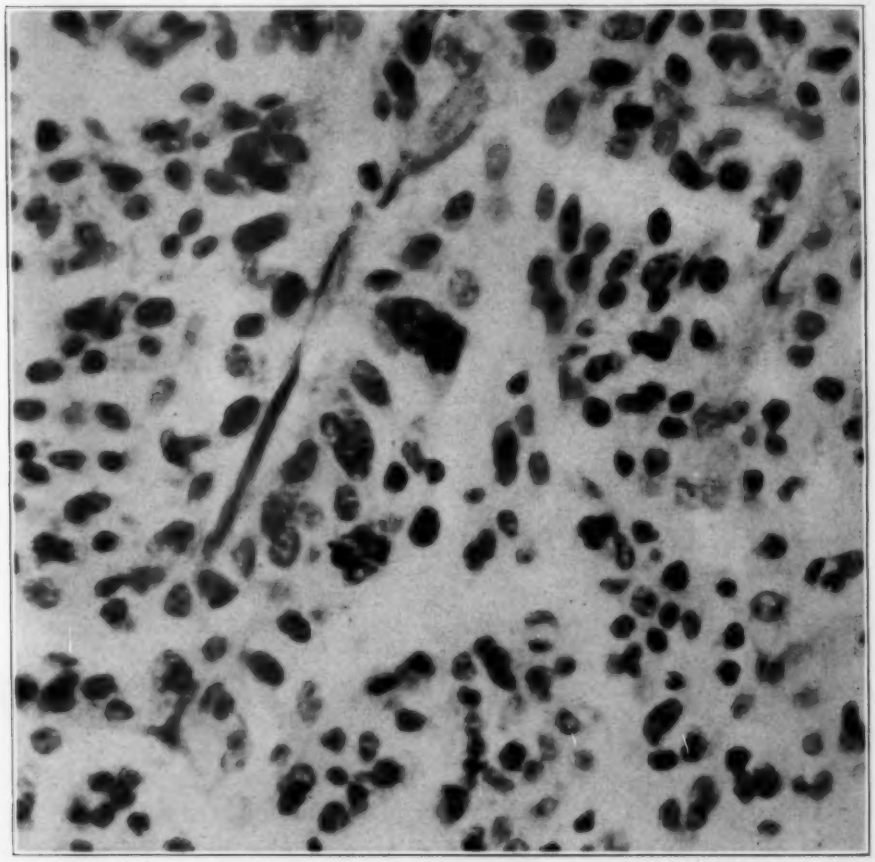

Fig. 13 (case 15).—A photomicrograph showing a tumor composed of round and polyhedral cells with numerous giant cells, probably of thymic origin.

in the rapid regression and disappearance of both the cervical and the mediastinal mass (fig. 10 *B*). The patient is clinically free from the disease at the time of writing, more than six years after the onset and one year after the last treatment. A review of the microscopic sections prepared in 1928 shows that the structure is composed essentially of cylindric cells in a plexiform arrangement. The nuclei are large and clear, with no nucleoli. In certain areas there are giant cells which resemble Hassall's corpuscles. The structure is consistent with a diagnosis of a tumor of thymic origin (fig. 11).

The unusual features of this case were: (1) that the patient was alive and clinically free from the disease nearly seven years after the onset; (2) the long interval of five years between the first treatment of the cervical adenopathy and the local recurrence, and (3) the radiosensitivity of the tumor at the time of the

Fig. 14 (case 16).—*A* shows the invasion of the soft parts over the anterior wall of the chest by tumors from a primary thymic tumor. *B* shows the same area three weeks after treatment.

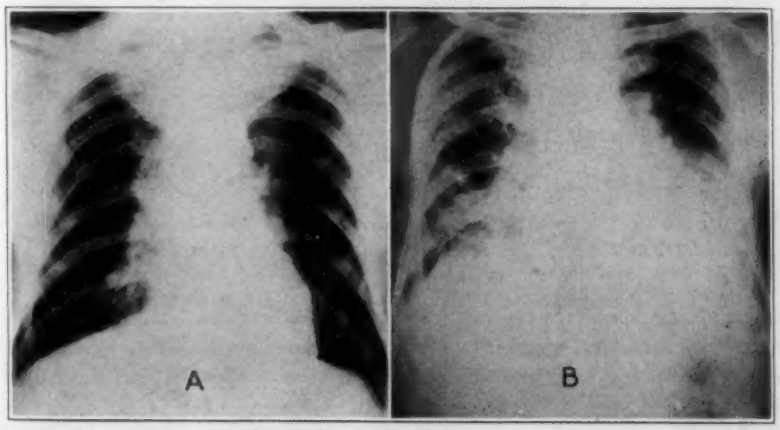

Fig. 15 (case 16).—Roentgenograms of the lungs. *A* shows a primary mediastinal thymoma; *B* shows an extension of the disease in the mediastinum six weeks later.

second irradiation. It is of special interest that the result was so good in spite of the high degree of radiosensitivity of the tumor. Usually those tumors which respond rapidly are so highly malignant that they are accompanied by a grave prognosis.

Case 15.—G. H., a man aged 39, had pain in the chest and in the back in August 1930. These symptoms were soon followed by dyspnea, cough, swelling of the neck, hoarseness and loss of weight. Examination revealed engorgement of the veins of the neck and physical signs of a mediastinal mass. Roentgen examination of the chest revealed a large mediastinal mass extending from the hilus of the left lung at the level of the third rib outward toward the periphery (fig. 12). The trachea was displaced markedly to the right. There were discrete enlarged nodes in both cervical areas and in the right axillary and right inguinal regions. High voltage roentgen therapy was instituted, but the patient's general condition grew worse, and he died two weeks after therapy was begun. Autopsy revealed a mediastinal tumor with extension to the pleura and the pericardium, metastases to the peritoneum, the liver and the pancreas and gangrene of the left lung.

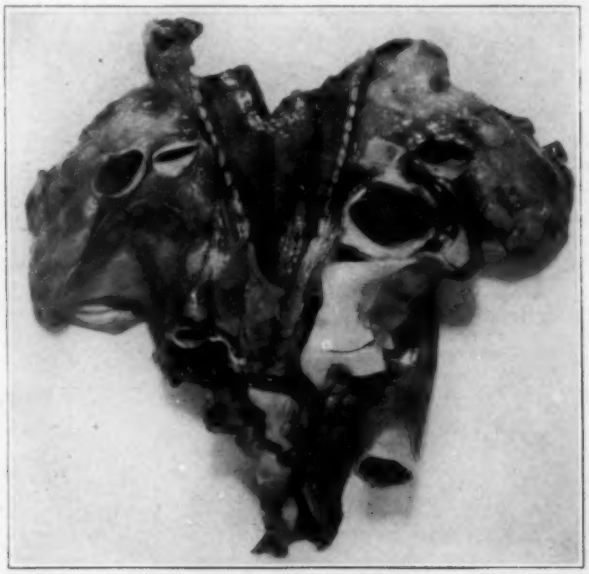

Fig. 16 (case 16).—A photograph of the gross specimen of a mediastinal tumor removed at autopsy. It appears to have originated in the thymus.

Examination of the microscopic sections revealed diffuse small round cell lymphosarcoma with occasional giant cells resembling Hassall's corpuscles (fig. 13). The failure of the lesion to respond to irradiation is probably best explained by the extent of the disease and by the poor general condition of the patient rather than by an inherent radioresistance of this particular type of tumor.

Case 16.—C. B., a man aged 44, was admitted to the hospital on Aug. 27, 1933, with a history that five months previously he noted nodular masses in the skin over the anterior wall of the chest. These were followed by the appearance of similar lesions in both axillae. Examination revealed multiple nodular tumors over the sternum and in both axillae and groins (fig. 14). Roentgen examination on August 28 disclosed a well defined tumor in the mediastinum, and a roentgenogram taken on October 13 showed marked advancement of the process (fig. 15).

Microscopic examination revealed a sarcoma composed of round and polyhedral cells, suggestive of thymic origin. Radium pack therapy was administered daily from September 9 to September 24, alternately to the upper and the lower portions of the sternum (at a distance of 15 cm., with a portal of 10 cm. and with a dosage of 50,000 mg. hours). This resulted in the disappearance of all the tumors. In spite of the local regression the patient soon became jaundiced. His general condition grew progressively worse, and he died thirty-seven days after treatment was begun.

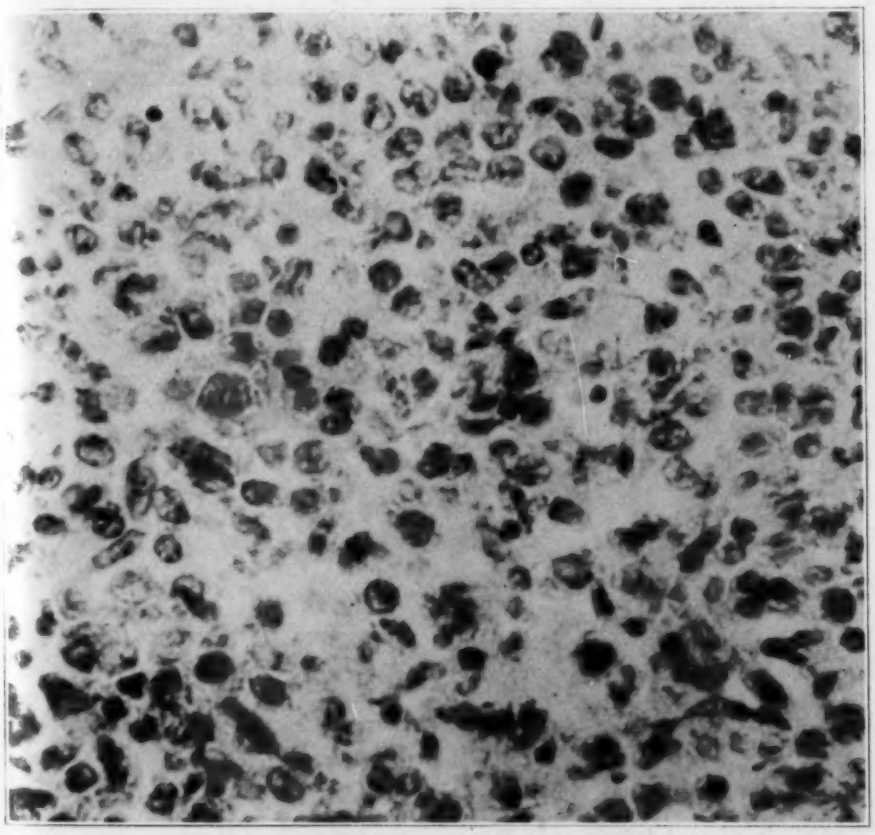

Fig. 17 (case 16).—A photomicrograph showing the structure of the thymic tumor depicted in figure 16, which was that of reticulum cell lymphosarcoma. The tumor proved to be highly radiosensitive, but treatment was followed by prompt recurrence, extension of the disease and death.

Autopsy revealed a severe degree of jaundice, cutaneous and subcutaneous tumor nodules and invasion of the lymph glands in the neck, axillae, groins, mediastinum and retroperitoneal areas. In the region of the thymus there was a discrete tumor which had the anatomic position of the thymus (fig. 16). Examination of the microscopic sections revealed a malignant tumor composed of round and polyhedral cells, growing diffusely, with numerous mitoses (fig. 17).

This case is an example of a rapid primary response to irradiation followed by prompt recurrence in a patient in whom the disease was widespread throughout the body.

CASE 17.—J. H., a man aged 43, was admitted to the hospital on March 8, 1933, with a history that in February 1932 he had dyspnea, weakness and pain in the chest, followed by cough, abdominal pain and the loss of 60 pounds (27.2 Kg.) over a period of six months. Three weeks before admission swelling of the sternum was noted, and one week before admission large masses appeared in both sides of the neck and in the right axilla. Examination revealed marked emaciation and a large, pyramid-shaped swelling of the upper two thirds of the sternum. There were enlarged, discrete nodes in both cervical and axillary regions. Roentgen examination of the chest revealed a large mediastinal mass extending widely in all directions (fig. 18 *A*). A lymph node was excised from the right axilla, which on microscopic examination revealed the typical structure of reticulum cell lymphosarcoma (fig. 19). Roentgen therapy resulted in prompt regres-

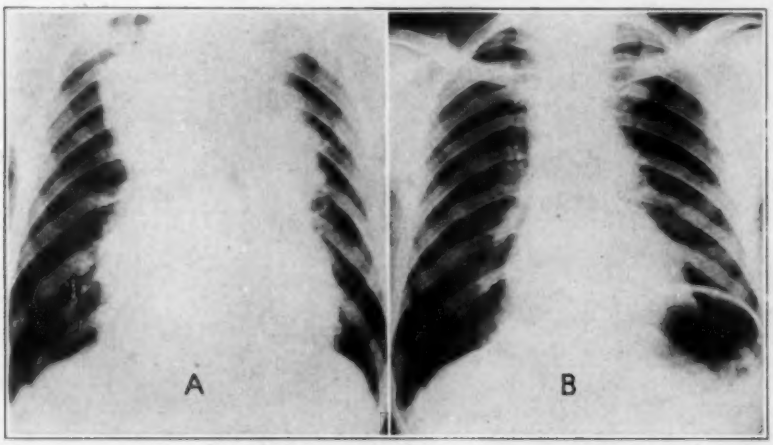

Fig. 18 (case 17).—Roentgenograms of the lungs. *A* shows a huge mediastinal mass before treatment; *B* shows the same area three months later, with almost complete disappearance of the lesion after roentgen therapy. This is an example of a highly radiosensitive lesion.

sion of the sternal tumor and mediastinal mass, as noted by repeated roentgen examination of the chest. The general condition of the patient improved, and his symptoms disappeared. Two months after treatment was begun there was a marked reduction in the size of the mediastinal mass, and three months after the beginning of treatment a roentgen examination of the chest revealed no demonstrable evidence of disease in the mediastinum (fig. 18 *B*). The patient was last seen in March 1934. His general condition was good, he had no disturbing symptoms, and a roentgenogram of the chest revealed a normal mediastinum (fig. 20).

The mass in this case is an example of a highly radiosensitive tumor which responded to roentgen therapy. It is of interest that whereas the mediastinal mass proved to be radiosensitive, it was not extremely so, as indicated by the fact that the roentgenogram of the chest made two months after

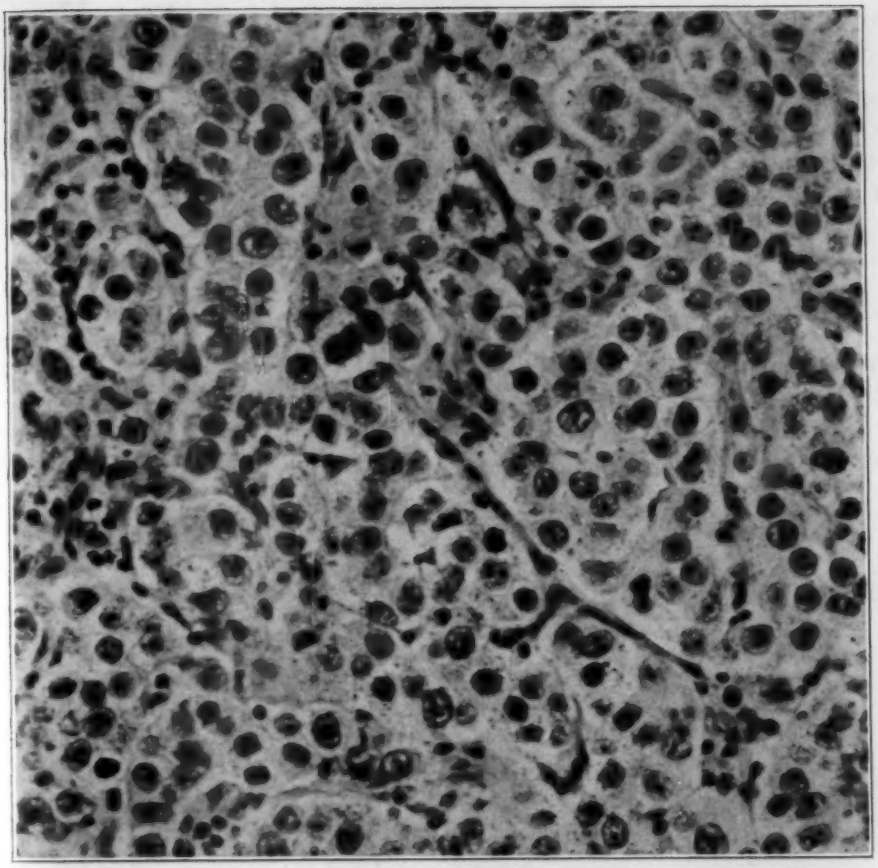

Fig. 19 (case 17).—A photomicrograph showing the structure of a reticulum cell lymphosarcoma, probably of thymic origin.

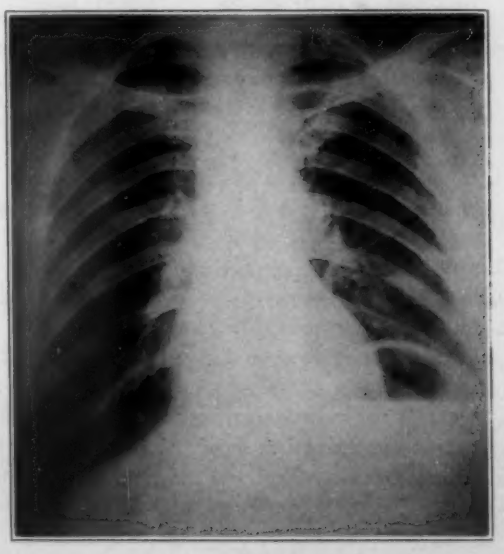

Fig. 20 (case 17).—A roentgenogram showing the appearance of the lungs fourteen months after treatment.

treatment failed to show complete regression. This is an example, therefore, of the better prognosis in cases of tumor which, although sensitive to radiation, do not regress too rapidly.

CASE 18.—W. C., a man aged 37, was admitted to the hospital on Aug. 21, 1930, with a history that six weeks previously he had begun to suffer from vague pains throughout the skeletal system, enlarged cervical glands, weakness and loss of weight. Examination revealed that the patient was markedly undernourished. The cervical and supraclavicular glands were enlarged, and roentgen examination of the chest revealed a widened mediastinal shadow (fig. 21). Microscopic examination of a lymph node revealed a structure resembling that of thymic carcinoma. The lesion failed to respond to irradiation. The patient's general condition became rapidly worse, and he died fifty days after admission.

The growth in this case is an example of the radioresistant form of thymic tumor. The microscopic structure was consistent with the failure of the growth to respond to treatment.

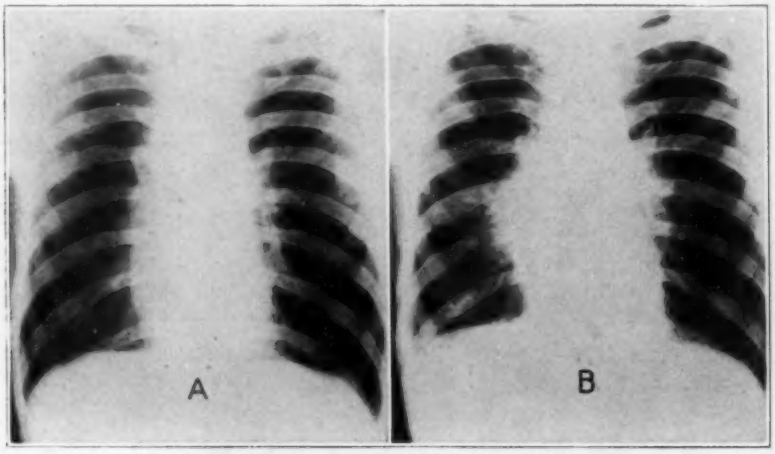

Fig. 21 (case 18).—Roentgenograms of the lungs. *A* shows a mediastinal mass, probably of thymic origin, before treatment; *B* shows the same area after treatment.

CASE 19.—W. P., a white man aged 34, was admitted to the hospital on June 2, 1932. Symptoms were present for fourteen months and consisted of pain, dysphagia, dyspnea, cough and attacks of fainting. The examination disclosed dilatation of the veins of the neck and chest, pleural effusion at the base of the right lung and enlarged axillary nodes. A biopsy specimen revealed a tumor composed of round and polyhedral cells with numerous giant cells (fig. 22). Roentgenograms of the chest revealed a marked accentuation of the mediastinal shadow on both sides and a pleural effusion on the right side (fig. 23). The tumor regressed rapidly, and on August 24 the mediastinum appeared to be normal. Three months later the disease recurred and the patient died. Autopsy revealed a tumor involving the axillary, mediastinal, retroperitoneal and mesenteric lymph nodes, with extension to the pleura and pericardium and metastases to the liver and spleen.

Case 20.—L. O., a white man aged 54, was admitted to the hospital on Sept. 13, 1932. His general health was good until three months prior to admission, at which time he began to have enlarged cervical glands, pain in the left side of the chest, dyspnea and cough and considerable loss of weight. The physical examination disclosed a marked bulging of the anterior wall of the chest on the left in the region of the border of the sternum. There were also an enlarged, firm, movable lymph node in the left supraclavicular region and enlarged glands in the left

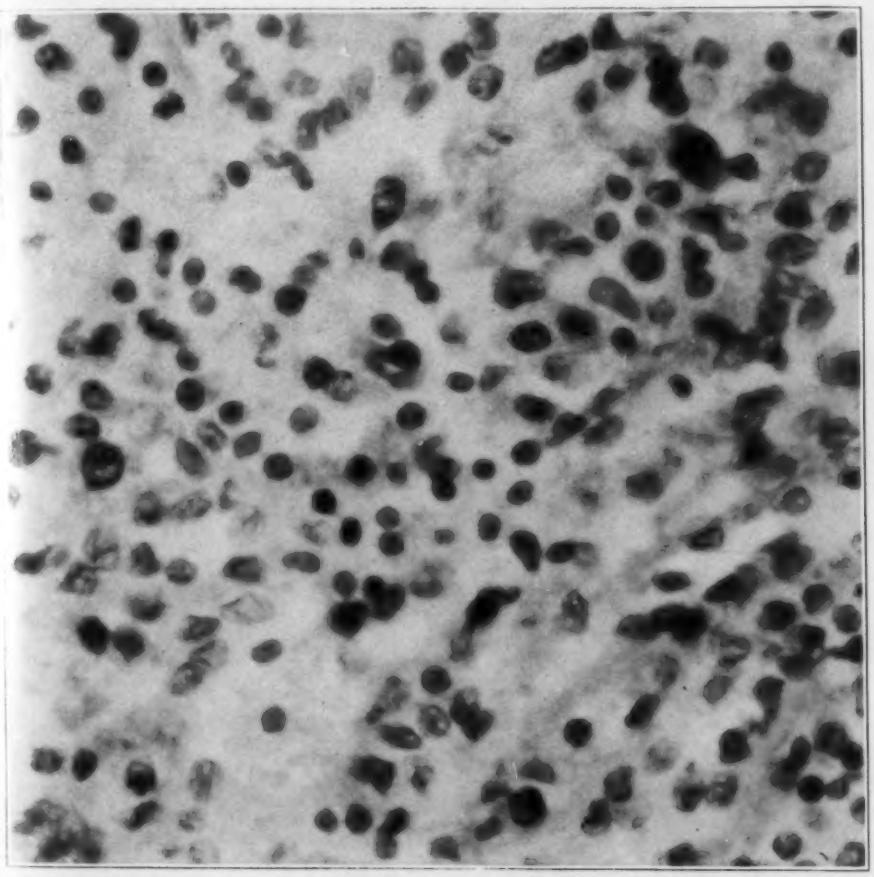

Fig. 22 (case 19).—A photomicrograph of a section of a tumor composed of round and polyhedral cells, with many giant cells present. The tumor was probably of thymic origin. The lesion responded rapidly to irradiation but recurred promptly.

axilla. The veins in the neck were markedly distended. Microscopic examination of tissue from the sternum revealed a structure typical of thymoma. Roentgenograms revealed an extensive mediastinal mass located chiefly on the left side. There was also considerable fluid in the left pleural cavity. One thousand cubic centimeters of dark, amber-colored fluid was withdrawn by paracentesis from the

left pleural sac. Roentgen treatment was instituted on September 30. There was slight clinical improvement, but the disease recurred promptly, and the patient died outside the hospital in January 1933, about three months after the first roentgen treatment.

CASE 21.—C. R., a white man aged 56, was admitted to the hospital on April 20, 1932. According to the history his neck began to swell two months prior to admission and rapidly increased in size, accompanied by cough and dyspnea. Examination revealed marked cervical adenopathy. Microscopic examination of the biopsy specimen revealed a thymic carcinoma (fig. 24). Roentgen examination of the chest revealed an abnormal shadow of heavy density superimposed on the upper portion of the mediastinum (fig. 25 *A*). The patient received two courses of high voltage roentgen therapy in April and May and in August and September. There was only moderate response to irradiation as shown by a slight diminution

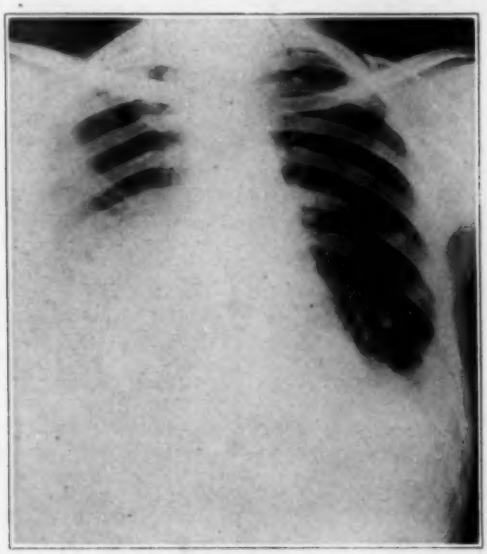

Fig. 23 (case 19).—A roentgenogram showing a tumor in the mediastinum and fluid at the base of the right lung.

of the mediastinal shadow (fig. 25 *B*). The patient committed suicide on October 4, after he was discharged from the hospital.

PRINCIPLES AND TECHNIC OF TREATMENT

It is evident from the gross anatomy of lymphosarcoma that comparatively large masses of tumor tissue must be exposed to radiation and that because of its widespread distribution extensive areas of the body must be treated. Were it not for the high degree of radiosensitivity of the tumor, the doses required to control the disease would be far greater than the general condition of the patient would tolerate. However, the degree of radiosensitivity is so high that relatively small

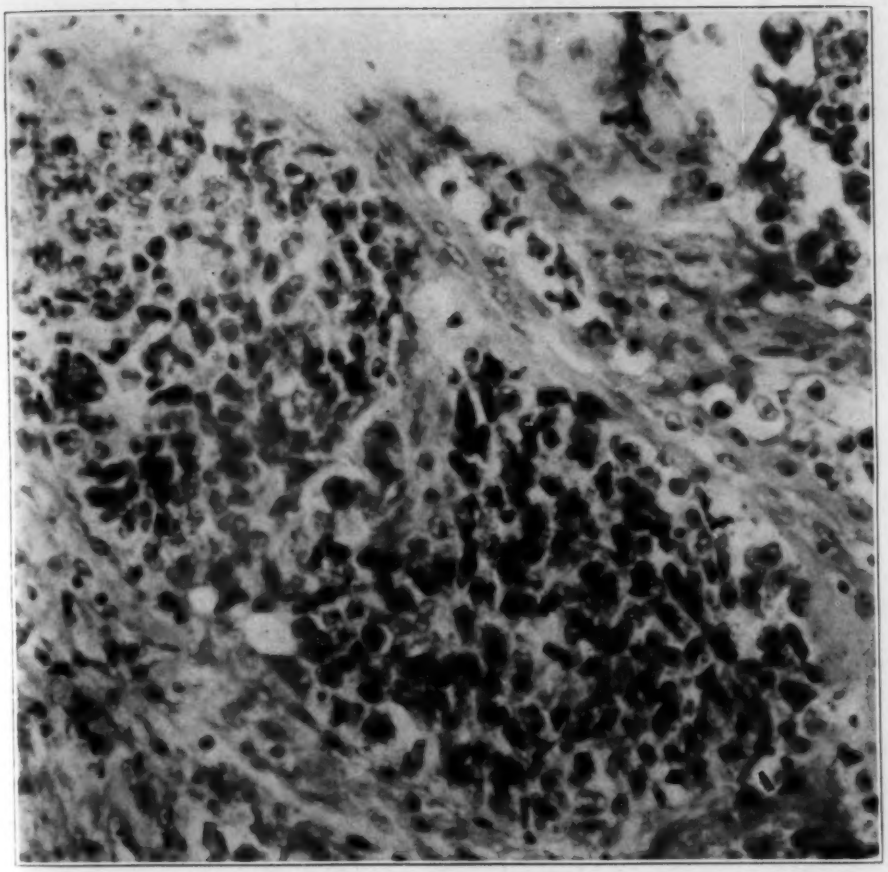

Fig. 24 (case 21).—A photomicrograph showing carcinoma of the thymus. The lesion proved to be radioresistant.

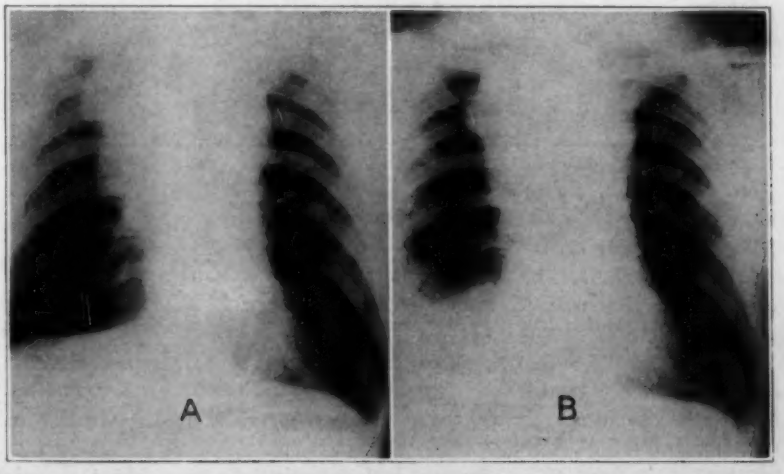

Fig. 25 (case 21).—Roentgenograms of the lungs. *A* shows a tumor in the mediastinum before treatment. The microscopic diagnosis was thymic carcinoma. *B* shows a slight diminution in the mediastinal mass following roentgen therapy. The lesion was essentially radioresistant.

doses can be administered effectively over widespread areas with no harmful effects.

The technic of roentgen therapy for lymphosarcoma and Hodgkin's disease has undergone various changes. When the transition from the lower to the higher voltage was made, massive doses were at first administered which caused many disastrous results. The desirability of fractionating the dose was soon established (Dresser,[24] Desjardins,[25] Voorhoeve[26] and Gilbert and Sluys[27]). The other development of importance was the recognition that the actual distribution of the disease is nearly always wider than the clinical examination discloses, and consequently wide areas must be irradiated in which the presence of the disease, though not clinically demonstrable, must be suspected.

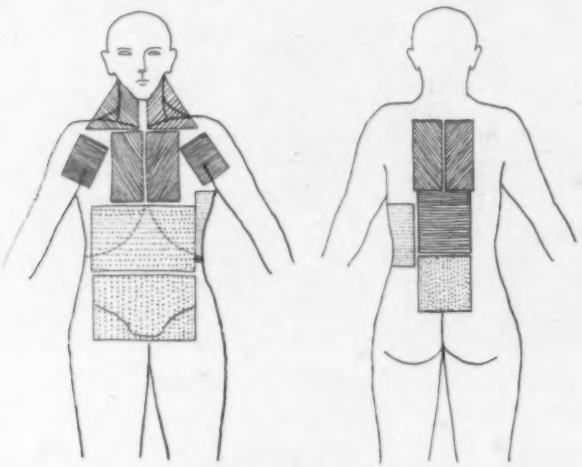

Fig. 26.—A diagram showing the lymph node areas to be treated in cases of lymphosarcoma (Gilbert and Sluys).

Gilbert and Sluys[27] elaborated a technic of roentgen therapy for malignant granuloma which has yielded interesting results.

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24. Dresser, R.: Lymphoblastoma (Hodgkin's Disease) of Sternum, Am. J. Roentgenol. **15**:525 (June) 1926; Lymphogranulomatose der Knochen (Hodgkinsche Krankheit), Strahlentherapie **41**:401, 1931.

25. Desjardins, A. U.: Radiotherapy for Lymphoblastoma, Radiology **7**:121 (Aug.) 1926; Rationale of Radiotherapy in Hodgkin's Disease and Lymphosarcoma, Am. J. Roentgenol. **17**:232 (Feb.) 1927.

26. Voorhoeve, N.: La lymphogranulomatose maligne; résultats obtenus par l'auteur avec la röntgenthérapie; les principes du traitement et leur application; Valeur de la biopsie pour le diagnostic, Acta radiol. **4**:567, 1925. On Granuloma Malignum, ibid. **5**:374, 1926.

27. Gilbert, R., and Sluys, F.: La radiothérapie de la granulomatose maligne, J. de radiol. et d'électrol. **17**:129 (March) 1933.

Figure 26 shows the fields which Gilbert and Sluys utilized. The factors were as follows: from 180 to 200 kilovolts, intensity of from 2 to 4 milliamperes and filtration with from 0.5 to 1 mm. of copper with the focal distance varying with the depth of the lesion and the

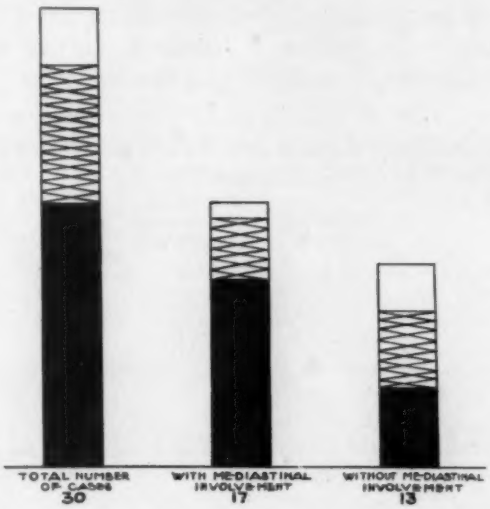

Fig. 27.—A chart showing the present condition of the patients with lymphosarcoma. The solid black areas indicate the number of patients who died; the cross-hatching, the number who are alive, but show evidence of the disease, and the white areas, the number who are living and are without symptoms.

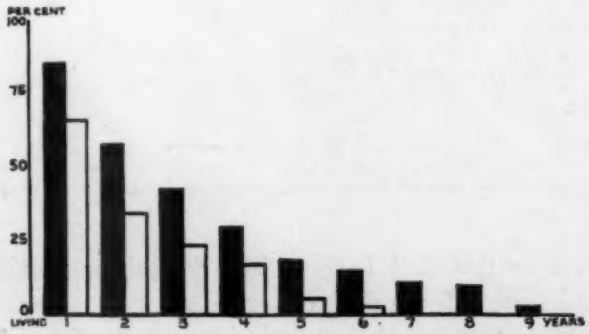

Fig. 28.—A chart showing the duration of the disease from the onset of symptoms in cases of Hodgkin's disease and lymphosarcoma. The black areas indicate the number of patients with Hodgkin's disease, and the white areas, the number with lymphosarcoma.

size of the field. The dose to each field in the first series was 400 r (roentgen). For the more superficial lesions in the cervical and axillary nodes the total dose was between 700 and 1,100 r. For mediastinal

lesions a dose of 1,000 r was administered to each of four portals, making a total of 4,000 r. The patient was treated daily, receiving 170 r at each treatment. When the lesion was extensive the dose during the first few days was diminished in order to avoid a toxic reaction. The treatment was continued once or twice a day for from four to five weeks. In certain cases in which the lesions proved to be resistant to roentgen therapy a response to distance massive radium therapy has been noted (Bowing,[28] Mallet[29] and Dautwitz[30]).

TABLE 2.—*Condition of Patients with Lymphosarcoma on Feb. 1, 1934*

	Mediastinal Involvement	Without Mediastinal Involvement	Total	Per Cent of Total
Alive, with symptoms	4	5	9	30
Alive, without disease	1	3	4	13
Deceased	12	5	17	57
Total	17	13	30	100

TABLE 3.—*Interval from the Onset of the Disease to Death in Cases with Fatal Outcome* *

Duration, Months	Mediastinal Involvement	Without Mediastinal Involvement	Total
0 to 6	4	0	4
7 to 12	3	2	5
13 to 18	3	0	3
19 to 24	0	1	1
25 to 30	0	1	1
31 to 36	0	1	1
37 to 42	0	0	0
43 to 48	0	0	0
49 to 54	1	0	1
Total	11	5	16

* One case could not be included in the study regarding duration, since death was caused by suicide.

With some exceptions I have utilized the principle of irradiating not only the lesions that are clinically evident but all lymph node areas which do not show clinical evidence of disease but which are regarded as potentially invaded. Irradiation is given daily for four or five weeks.

28. Bowing, H. H.: Value of Radium and X-Ray Therapy in Hodgkin's Disease, J. Radiol. **2**:20 (Dec.) 1921.

29. Mallet, L.: Curiethérapie: Technique physique et posologie: Application aux principaux cancers, Paris, J. B. Baillière et fils, 1930, p. 300.

30. Dautwitz, F.: Lymphogranulomatose und Radiumbestrahlung, Strahlentherapie **25**:375, 1927.

RESULTS

The length of time that elapsed between the onset of symptoms and the beginning of treatment in this series of cases varied from one month to three years, the average interval being ten months. In 17 of the 30 patients there was roentgenologic evidence of mediastinal involvement, and in 13 the mediastinum appeared to be normal. Table

TABLE 4.—*Interval from the Onset of the Disease to Feb. 1, 1934, in Cases in Which the Patients Are Living*

Duration, Months	Mediastinal Involvement	Without Mediastinal Involvement	Total
7 to 12	1	0	1
13 to 18	1	1	2
19 to 24	1	3	4
25 to 30	0	0	0
31 to 36	0	0	0
37 to 42	1	0	1
43 to 48	0	1	1
49 to 54	0	2	2
55 to 60	0	0	0
61 to 66	0	0	0
67 to 72	0	1	1
73 to 78	0	0	0
79 to 84	1	0	1
Total	5	8	13

TABLE 5.—*Interval from the Onset of the Disease for All Patients Living and Dead*

Duration, Months	Mediastinal Involvement	Without Mediastinal Involvement	Total
0 to 6	4	0	4
7 to 12	4	2	6
13 to 18	4	1	5
19 to 24	1	4	5
25 to 30	0	1	1
31 to 36	0	1	1
37 to 42	1	0	1
43 to 48	0	1	1
49 to 54	1	2	3
55 to 60	0	0	0
61 to 66	0	0	0
67 to 72	0	1	1
73 to 78	0	0	0
79 to 84	1	0	1
Total	16	13	29

2 and figure 27 show the condition at the time of writing of the patients with and those without mediastinal involvement.

DURATION OF LIFE

The period from the onset of symptoms to death or, in the case of patients still alive, to Feb. 1, 1934, ranged from two months to six years and eight months. In the cases with fatal outcome the minimum period of survival was two months and the maximum, four years and

five months. The average or mean period was approximately sixteen months (table 3).

For the patients alive on Feb. 1, 1934, the minimum interval from the onset of symptoms was ten months and the maximum, six years and eight months. The average interval was three years (table 4).

If one includes all patients both deceased and living, the average interval from the onset of symptoms to death or to Feb. 1, 1934, was twenty-five months, or approximately two years (table 5).

A study of 100 patients with Hodgkin's disease is at present under way, and it seemed interesting to compare the data relating to the duration of the disease in that group with the duration in the group with lymphosarcoma. It is evident from table 6 and figure 28 that patients suffering from Hodgkin's disease live somewhat longer than those suffering from lymphosarcoma.

TABLE 6.—*Comparative Figures on Interval from the Onset of the Disease to Death or to Feb. 1, 1934, in Cases of Hodgkin's Disease and of Lymphosarcoma*

	Lymphosarcoma		Hodgkin's Disease	
Alive	Cumulative Frequency	Per Cent	Cumulative Frequency	Per Cent
0 to 3 months	29	100	80	100
4 to 6 months	28	97	80	100
7 to 12 months	25	86	80	100
13 to 24 months	19	66	69	86
25 to 36 months	10	34	46	58
37 to 48 months	7	24	34	43
49 to 60 months	5	17	24	30
61 to 72 months	2	7	15	19
73 to 84 months	1	3	12	15
85 to 96 months	0	0	9	11
97 to 108 months	0	0	8	10
109 to 120 months	0	0	2	3

COMMENT

Lymphosarcoma can be divided into two major clinical groups: (1) a generalized form, with widespread involvement of the lymph nodes, and (2) a localized form, in which a single group of lymph nodes or a localized area of lymphoid tissue is the seat of the disease. The generalized form is more common, the localized form comparatively rare. In my group of 30 cases the ratio was 5:1 (25 of the diffuse form and 5 of the localized form).

The generalized form of the disease usually attacks the superficial and deep lymph nodes throughout the body. Sometimes the mediastinal nodes are extensively invaded, giving rise to a large mediastinal tumor. In this series of 30 cases 17 patients, or 56 per cent, showed roentgenologic evidence of mediastinal disease, and among 13 cases which came to autopsy, gross and microscopic evidence of mediastinal involvement was seen in 9. The absence of positive roentgenologic evidence of mediastinal involvement does not necessarily indicate the absence of

disease, and in view of the high percentage of involvement in the mediastinal nodes as proved by autopsy, this area must be regarded as potentially involved and must be treated accordingly.

The same principle holds true for the retroperitoneal and mesenteric regions. The lymph nodes of these regions proved to be involved in 11 of the 13 patients who were examined at autopsy (85 per cent), with involvement of the retroperitoneal glands in 8 and of the mesenteric glands in 3. This circumstance renders it essential to regard the mesenteric and retroperitoneal areas as potentially involved, and they must be treated accordingly regardless of the absence of the disease on clinical examination.

The localized form of the disease occurred in 5 patients. In 2 the disease originated in the nasopharynx and extended upward to the accessory sinuses. Both died; at autopsy no other evidence of disease was discovered in 1, and the second patient died without showing other clinical evidence of disease. Two patients with lymphosarcoma of the rectum are well after two years and three years, respectively, without showing further evidence of the disease at any time. The fifth patient was treated two years ago for a mass of nodes localized in the left cervical region. The lesion disappeared under irradiation, and there has never been evidence of the disease in any of the other lymphoid structures.

When the mediastinum shows extensive involvement, the clinical and roentgenologic features are such as to simulate tumors of thymic origin. The histogenesis of the thymic parenchyma being undetermined, it is not feasible to classify these tumors. Some authors divide thymic tumors into lymphosarcoma and carcinoma; others designate the whole group by the term thymoma. Regardless of their histogenesis, however, one fact is certain: From the point of view of radiosensitivity they form two distinct and separate groups. One is highly radiosensitive and the other markedly radioresistant.

The radiosensitive forms comprise two histologic types: (1) the small round cell type, or malignant lymphocytoma, and (2) the large round cell type, or reticulum cell lymphosarcoma. The small cell type is exceedingly rare. According to Haagensen [22] it occurs usually in children, occupies the thymic region and metastasizes widely. The large round cell type occurs much more frequently. The histogenesis of this type is disputed, some believing that it arises in the anterior mediastinal lymph nodes and others that it originates in the thymus.

The radioresistant thymic tumors present a varied histologic structure. In some the cells are large and flat, in some places forming structures which resemble Hassall's bodies. In others the cells are arranged in alveoli and present a definite glandular structure. In most examples the structure is mixed, and one finds alveolar areas, polyhedral cells and

lymphocytes enmeshed in a dense connective tissue stroma. In some tumors the cells lining the alveoli are cylindric (fig. 11).

The difference in the radiosensitivity of the two groups of mediastinal tumors intimately connected with the thymus is so striking that a moderate dose of external radiation constitutes a valuable therapeutic test in differentiating between the two forms.

The principles of treatment of lymphosarcoma differ for the generalized and localized forms. In the case of the generalized form, wide areas are exposed to radiation and all areas bearing lymph nodes are treated, regardless of the distribution of the disease that is evident on clinical examination. In view of the extensive areas of the body that must be exposed to radiation and because of the marked radiosensitivity of the lesion, the doses over each portal of entry are relatively small compared to those utilized in the treatment of the epidermoid carcinomas. The rapidity with which the exposures are made is guided by the general condition of the patient.

The principle of treatment of the localized form differs from that for the generalized form. Because of the limited extent of the disease, it is safe to deliver a much larger dose of radiation. Although under these circumstances it is not necessary to simulate the large doses used in the treatment of carcinoma, the dose should be much larger than that which can be administered safely in cases of the generalized form of the disease. Thus, for example, the patient with a localized mass of cervical lymph nodes and no other clinical evidence of disease received 80,000 mg. hours of radium at a distance of 10 cm. over a surface area 10 cm. in diameter during a period of three weeks.

The question naturally arises as to the differentiation of the localized from the generalized forms of the disease when only a single focus can be detected on clinical examination. I know of no method by which it can be predicted that the appearance of a localized focus of the disease will or will not be followed by the appearance of the disease in other areas. This difficulty raises the important question of whether it may not be an expression of sound judgment to irradiate prophylactically all lymphoid areas regardless of how limited the disease may appear to be on clinical examination. No general rule can be made on this point, but each case should be considered on an individual basis with these facts in mind.

The results of roentgen therapy of lymphosarcoma may be summarized briefly. In the generalized form the disease may be arrested for varying periods and may sometimes be controlled for several years. In the rare localized forms the disease can be eradicated. This result is sometimes followed by the appearance of the disease elsewhere in the body, but occasionally an apparent cure can be accomplished, the patient remaining well and free from the disease for as long as ten years.

SUMMARY AND CONCLUSIONS

Thirty cases of microscopically proved lymphosarcoma are reported.

Thirteen patients died in the hospital, and all came to autopsy. The pathologic observations are presented.

Seventeen, or 57 per cent of the group, are dead. The minimum duration of life from the onset of symptoms to death was two months, the maximum duration, four years, and the average duration, sixteen months.

Of the 13 patients alive 9 show clinical evidence of the disease and 4, or 13 per cent, show no evidence of the disease.

For the patients alive, the minimum interval from the onset of symptoms to Feb. 1, 1934, was ten months, the maximum, six and one-half years and the average, three years.

Including all cases, the average interval from the onset of the disease to death or to Feb. 1, 1934, was approximately two years.

For the 4 patients who are alive and clinically free from the disease, the interval of freedom from the disease varies between two and six years.

Twenty-three of the 28 patients treated by irradiation, or approximately 80 per cent, were benefited by the treatment. Regression of the tumors, relief from the pain and improvement in the general condition of the patient constituted the immediate primary results following treatment.

The disease has a notorious tendency to recur, and more particularly to reappear in outlying areas. Prophylactic irradiation to lymph node areas which are not clinically involved may help to diminish this tendency. There is some evidence that the pursuit of this principle has averted the danger in some instances.

NEUROFIBROMA OF THE URETER

REPORT OF A CASE WITH OPERATION AND RECOVERY

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BROOKLYN

When one considers the ureter merely as a muscular duct which transmits the urine secreted and excreted by the kidney into the bladder, it is not surprising that one finds so few instances of primary tumor of this organ. The majority of the neoplasms involving the ureter are papillary carcinomas which originate in the pelvis of the kidney and the cells of which break off and implant themselves on the mucosa of the ureter. Whereas benign papilloma occurs rather infrequently in the pelvis of the kidney, it is still rarer for such a growth to spread secondarily along the ureter until after it has become malignant. Primary carcinoma of the ureter is also rare, only sixty-one cases having been reported in the literature.

Careful perusal of the literature failed to reveal a single case analogous to the one here reported, even though involvement of almost every other organ in the body by this type of tumor had been reported by various authors.

REPORT OF CASE

J. B., an Italian stevedore, aged 50, married, was referred by Dr. Bendetson on Nov. 20, 1930. The history was unessential except for uncomplicated gonorrheal urethritis ten years before. Several months previously he began to have slight backache, principally on the left side. For the preceding four weeks the patient had considerable pain in the left iliac region radiating down to the groin and testis and upward to the left flank. The pain was more or less constant, but was worse at night and frequently severe enough to keep him awake. At times he had attacks of fairly severe pain, but never severe enough to require a hypodermic injection. There were no urinary disturbances except nocturia two or three times. There was no macroscopic hematuria, although urinalysis revealed a few erythrocytes.

Physical examination revealed a swarthy, well nourished, obese and muscular man. The heart sounds were distant but of fairly good quality. There was slight tenderness over the left costovertebral region and, on deep palpation, in the left lower quadrant. No masses could be felt.

The bladder urine showed a specific gravity of 1.018, was clear, gave a positive reaction for acid and albumin and a negative reaction for sugar and contained a rare erythrocyte, an occasional leukocyte, a rare hyaline cast and an occasional epithelial cell. It contained no bacteria.

On examination by rectum the prostate was practically normal. Roentgen examination revealed both kidneys to be slightly enlarged, though the outlines were not very clear owing to the large size and muscularity of the patient. No

calculi were seen in the urinary tract. After careful study, on the left side of the spine above the iliac crest a faintly outlined, irregular shadow the size of a tangerine was seen, the nature of which could not be determined.

Cystoscopy revealed a definite lip formation of the median lobe of the prostate and normal lateral lobes, and also a normal bladder mucosa. The orifice of the right ureter was normal; that of the left was slightly injected. Indigo carmine, injected intravenously, appeared in five minutes from the right orifice; none had appeared at the end of ten minutes from the left. A no. 6 F wax-tipped catheter was passed up the left ureter, meeting marked obstruction 15 cm. and an impassa-

Fig. 1.—Retrograde pyelogram showing the dilated renal pelvis, dilatation and kinking of the upper portion of the ureter and the tip of the catheter obstructed at the upper margin of the tumor, which extends around the ureter from the third lumbar vertebra down to the sacro-iliac synchondrosis. Note the apparent failure to visualize the lower calix.

ble obstruction 24 cm. from the bladder. No scratch was seen on the wax tip. Later a no. 5 F catheter was passed and met the same impassable obstruction at 24 cm. A left retrograde pyelogram (fig. 1) revealed a markedly dilated renal pelvis with obliteration of the calices and a possible filling defect or failure to outline the lower calix and lower quarter of the pelvis, giving the impression of a mass involving the lower pole of the left kidney. The upper 6 cm. of the ureter was kinked and dilated to the size of a finger. Below this the ureter was

very narrow and showed a slight angulation at the lower level of the synchondrosis. The inferior margin of the mass in the film corresponded to the obstruction met by the catheter 15 cm. from the bladder. No urine was obtained from the left kidney.

A diagnosis of tumor of the left ureter secondary to a possible intrapelvic tumor was made, and nephro-ureterectomy was advised.

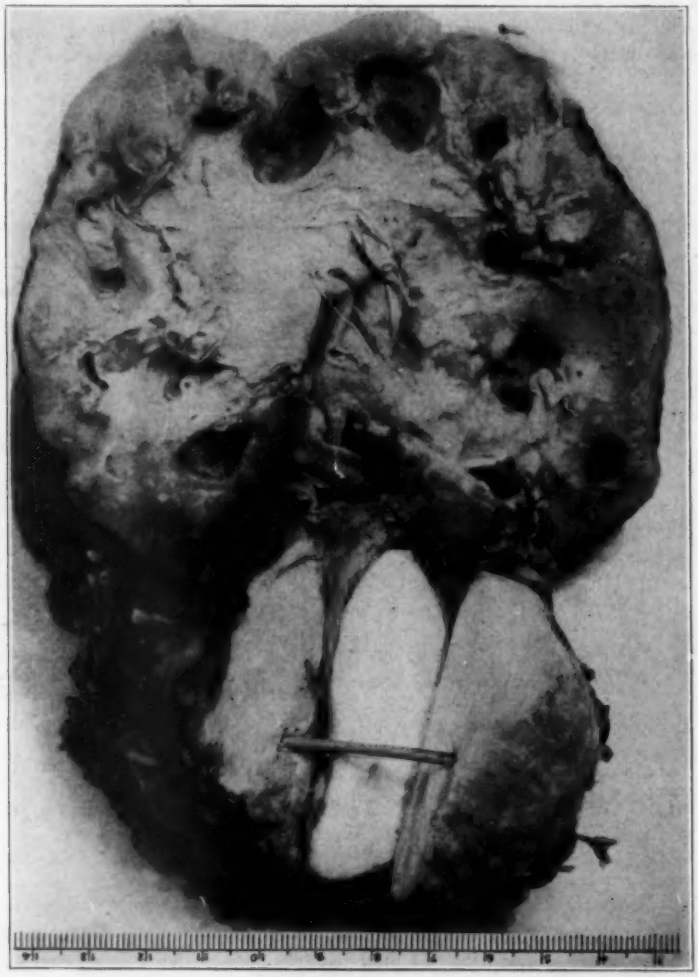

Fig. 2.—Cross-section showing the dilated renal pelvis and calices and also the large tumor surrounding the ureter. Note the dilated portion of the ureter at the upper border of the neoplasm, which narrows rapidly as it runs through the mass.

Two days later the patient entered the Jewish Hospital of Brooklyn, where, on November 24, intravenous pyelography showed a fairly normal right renal pelvis and ureter, but no dye was seen in the left renal pelvis or ureter. A mass of soft tissue the size of a tangerine was noted opposite the fourth lumbar vertebra.

A blood count showed: 7,300 leukocytes, 4,750,000 erythrocytes and 70 per cent hemoglobin. Chemical examination of the blood showed: sugar, 122 mg. per hundred cubic centimeters; creatinine, 2 mg.; urea nitrogen, 22.8 mg., and uric acid, 6 mg. The phenolsulphonphthalein test showed an excretion of 52 per cent for the first hour and 32 per cent for the second hour, making a total output of 84 per cent. The reactions to the Wassermann and Kahn tests were negative. The blood pressure on admission was 170 systolic and 110 diastolic.

Fig. 3.—A section showing the arrangement of the fibers in irregular bundles. Hematoxylin-eosin stain; × 100.

On November 26, with the patient under spinal anesthesia later reenforced by a small quantity of ether, a hockey stick incision was made over the left kidney from the costovertebral angle to the anterior iliac portion of the spine. The kidney was mobilized and found to be slightly enlarged, smooth, anemic, distended and thinned out in several areas. The pelvis and the upper 8 cm. of the ureter were very thin and distended with urine. The upper part of the ureter was the size of a thumb. The vascular pedicle, which was somewhat elongated but otherwise normal, was clamped, tied and cut. The ureter was followed downward below the dilated portion, where it was found to run directly into the middle of a large,

irregular, stony-hard mass the size of a tangerine, which was so adherent to the adjacent tissues by thick bands and adhesions that it was finally freed with the greatest difficulty and excised after each band was clamped and tied. The ureter was clamped, tied and severed below the mass. The peritoneum was carefully avoided. The wound was then closed in layers around two cigaret drains.

Except for some abdominal distention, oliguria and slight elevation of temperature for several days, the postoperative course was smooth. The blood pressure

Fig. 4.—A section showing the nerve fibers. Silver stain; × 100.

during the three days following operation ranged between 110 and 140 systolic. The blood urea nitrogen and creatinine values were 62.4 and 3.1 mg., on December 1, and 27.7 and 2 mg. on December 4. Owing to a slight cardiac disturbance the patient was kept in bed until December 9, the fourteenth day after operation. The wound healed by primary union, and the patient was discharged on December 13 in good condition.

The pathologic report was made by Dr. M. Lederer. Macroscopically the left kidney weighed 120 Gm. The capsule stripped off easily, and the surface was smooth except for many small cysts containing clear fluid. The surface was

mottled red, and one area was depressed. A section showed a diffusely yellow appearance. The normal renal tissue had been replaced by numerous dilated sacs (fig. 2).

The normal line of demarcation between the cortex and the medulla was absent. In some areas the renal tissue measured only 3 cm. in width. The pelvis was infiltrated by yellow tissue and was greatly dilated and thin. Microscopically the kidney showed the usual lesions of hydronephrosis.

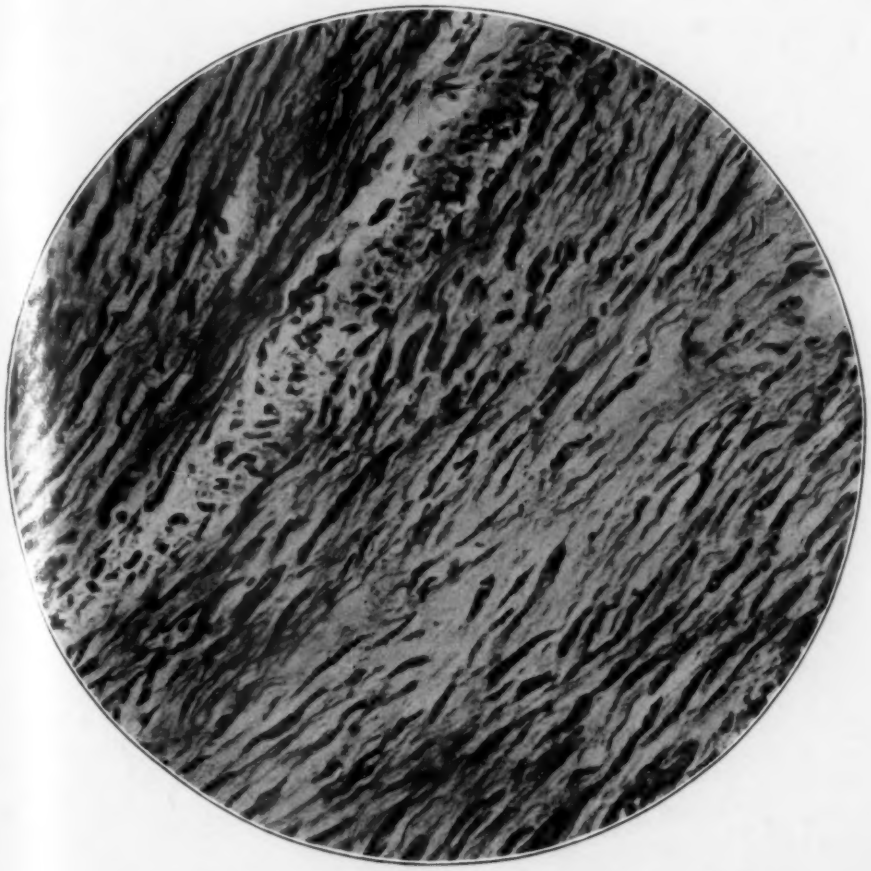

Fig. 5.—The same section as that shown in figure 4; × 450.

Macroscopically the ureter was surrounded by an irregular mass, 8 cm. in its longest diameter, which completely constricted the lumen of the ureter. From the surface of the mass projected several smaller nodules, each about 2 cm. in diameter, which on section were shown to be made up of dense yellow-gray tissue. The main mass was directly continuous with the ureteral wall, which was thinned both above and below the involving tumor. The major portion of the ureteral wall was markedly embedded in the surrounding mass of interlacing bundles of gray tissue, so that it could not be dissected from the latter.

Microscopically the tumor was made up of numerous bundles composed of interlacing fibers. The fibers gave a positive reaction on staining for nerve cells. The arrangement of the cells was in large masses separated from each other by a small amount of connective tissue stroma. In some areas the cells assumed large proportions, resembling nerve cells (figs. 3, 4 and 5).

The diagnosis was neurofibroma of the ureter.

CONCLUSION AND SUMMARY

This unique case is presented for the following reasons: 1. Primary tumors of the ureter are very rare. 2. No tumor of this kind involving the ureter has been found reported in the literature.

Correct preoperative diagnosis of the tumor was made by means of a wax-tipped catheter and by a retrograde pyelogram. The erroneous impression of a concomitant pelvic tumor was created by the pelvic outline, which showed an irregular mass in the lower portion of the renal pelvis.

This case demonstrates the futility of the present-day tendency among many physicians to depend entirely on intravenous pyelography for the diagnosis of all pathologic conditions of the urinary tract.

There was an amazing freedom from symptoms until a short time before the operation in spite of the fact that the large tumor had been gradually increasing its encroachment on the ureteral lumen, with destruction of the kidney parenchyma.

The success of early operation is apparent. The patient was alive and well in January 1934, when last heard from through Dr. Bendetson.

The general practitioner should be as suspicious of vague urologic conditions as he is of a pathologic condition in the breast. It is only through early diagnosis and treatment that satisfactory results can be hoped for.

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CHOLECYSTOGASTROSTOMY AND HEPATITIS

AN EXPERIMENTAL STUDY

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NEWPORT NEWS, VA.

Increased interest in surgical intervention on the gallbladder has resulted in the removal of cholecystogastrostomy from the class of serious, much feared and seldom performed operations to that of operations which are considered less serious and with which every surgeon has had experience. Its wider use has been hindered by a fear that infection of the liver may occur as a sequel. Many investigators have tried both experimentally and clinically to avoid this and other sequelae. This study is an experimental attack on the problem of hepatic infection following cholecystogastrostomy from a new point of view. Some light is thrown on the general pathologic problem of hepatic infection.

REVIEW OF THE LITERATURE

Experimentally, the gallbladder has been anastomosed to the alimentary tract at various points of the stomach, duodenum, jejunum and colon. Many studies have been made to determine which method will yield as nearly a physiologic result as possible and avoid undesirable accompaniments of such a procedure. The first cholecystenterotomy was done by von Winiwarter [1] of Liege; it was a short-circuiting operation which consisted in joining the gallbladder to the colon in seven stages over a period of sixteen months (from 1880-1881).

Oddi [2] (1887), in his study of the effect of bile on gastric acidity, performed perhaps the first cholecystogastrostomy experimentally, using the dog. He came to the conclusion that bile in the stomach before or after digestion does not affect the acidity or diminish the quantity of gastric juices. He observed that bile caused no alterations of the gastric content. He prophesied the use of cholecystogastrostomy in certain cases of disease of the gallbladder. Dastre [3] (1890), Cannac [4] (1897),

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1. von Winiwarter, A.: Ein Fall von Gallenretention bedingt durch Impermeabilität des Ductus choledochus Anlegung einer Gallenblasen-Darm Fistel, Heilung, Prag. med. Wchnschr. **7**:201 and 213, 1882.

2. Oddi, R.: Action de la bile sur la digestion gastrique étudiée au moyen de la fistule colécisto-gastrique, Arch. ital. de biol. **9**:138, 1888.

3. Dastre, A.: Recherches sur la bile, Arch. de physiol. norm. et path. **2**: 315, 1890.

4. Cannac, L. B.: De la cholécystogastrostomie, Thèse de Bordeaux, 1897, p. 62.

Masse [5] (1898) and Beaver [6] (1929) performed similar experiments and arrived at the same conclusion in relation to the gastric content. Beaver also found that the emptying time of the stomach following cholecystogastrostomy was the same as in the normal dog. Mocquot [7] (1911), Wiedemann [8] (1914) and Grey [9] (1916) performed cholecystogastrostomies and investigated the effect of bile on gastric digestion. The unanimous conclusion was that bile does not affect gastric digestion. In view of the newer ideas in regard to the interchange of duodenal and gastric content, the presence of bile in the stomach of a normal person is now accepted, and the discharge of bile into the stomach following cholecystogastrostomy is therefore not regarded as an important physiologic distortion. Beaver [6] and Grey [9] studied separately the acidity of gastric juice before and after this operation, and both found that bile in no way affects the gastric acidity. Bogoras [10] (1925) advocated the use of cholecystogastrostomy as a means of controlling gastric acidity by allowing the bile to flow into the stomach. Following the work of Graham [11] (1918), in which he showed rather conclusively that hepatitis is a constant accompaniment of cholecystitis, Gatewood and Poppens [12] (1922), Lehman [13] (1924) and Horsley [14] (1927) studied the effect on the liver and the biliary tract of cholecystogastrostomy. In his experiments Lehman attempted to remove all lymphatic connections between the liver and the gallbladder. All of these authors concluded that the liver and biliary tract always became infected in the dog following this operation. Weinberg, Wallin and Binger [15] (1927) found

5. Masse, E.: De la cholecystogastrostomie, Gaz. hebd. d. sc. méd. de Bordeaux **19**:534, 1898.

6. Beaver, M. G.: Cholecystogastrostomy: An Experimental Study, Arch. Surg. **18**:899 (March) 1929.

7. Mocquot, Pierre: Anastomose de la vésicule biliaire avec l'estomac et avec le duodénum, Compt. rend. Soc. de biol. **2**:118, 1911.

8. Wiedemann, H.: Experimentelle Untersuchungen zur Lehre der Verdauung und Resorption verschiedener Nahrungsprodukte bei anormalen Gallenzufluss in den Verdauungsapparat, Beitr. z. klin. Chir. **74**:594, 1914.

9. Grey, E. G.: An Experimental Study of the Effect of Cholecystogastrostomy on Gastric Acidity, J. Exper. Med. **33**:15, 1916.

10. Bogoras, N.; Cholecystogastrostomy in Gastric Ulcer; Operative Method for Treatment of Gastric Ulcer, Arch. f. klin. Chir. **134**:42, 1925.

11. Graham, E. A.: Hepatitis: A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521, 1918.

12. Gatewood, and Poppens, P. H.: Cholecystenterostomy from an Experimental Standpoint, Surg., Gynec. & Obst. **35**:445, 1922.

13. Lehman, E. P.: Hepatitis, Following Cholecystogastrostomy, Arch. Surg. **9**:16 (July) 1924.

14. Horsley, J. S., Jr.: Experimental Study of Cholecystogastrostomy and Cholecystoduodenostomy, South. M. J. **20**:669, 1927.

15. Weinberg, J. A.; Wallin, S. P., and Binger, M. W.: Gallbladder-Stomach Anastomosis, Surg., Gynec. & Obst. **44**:795, 1927.

hepatic infections invariably in dogs but not in a single monkey after cholecystogastrostomy.

It was not long after Oddi [2] suggested the use of cholecystogastrostomy in disease of the gallbladder that it was used clinically. As early as 1889, Mayo-Robson [16] performed what is now regarded as perhaps the first cholecystogastrostomy. However, the first cholecystogastrostomy with survival of the patient was done for stricture of the common bile duct in 1892 by Wickhoff and Angelberger [17] of Vienna, who thus furnished the first clinical data as to the tolerance of the stomach for bile. About this time Terrier [18] and Bardenheurer,[19] at the suggestion of Cozi, first used the duodenum in a short-circuiting operation to join the gallbladder to the intestinal tract.

Cholecystogastrostomy was performed by Terrier [18] (1896), Monod [20] (1896), Jaboulay [21] (1898) and Montognon and Duchamp [22] (1899) with favorable results in cases of tumors of the pancreas. Perrin [23] (1902) advocated the operation because of its nearness to anatomic and physiologic perfection as well as because of its simplicity. Eichmeyer [24] (1910) and Kohr [25] (1914) had early favorable experiences with the procedure, the latter having up to 1914 performed over sixty operations and published the reports of over one hundred. Jacobson [26]

16. Mayo-Robson, A. W.: A Case of Cholecystenterostomy, Med.-Chir. Tr., London **73**:61, 1890.

17. Wickhoff, M., and Angelberger, F.: Cholelithiasis; Obdurater Ductus Choledochi(?) Cholecysto-Gastrostomie, Heilung, Wien. klin. Wchnschr. **6**:325, 893.

18. Terrier, M.: Sur un cas de gastrocystentérostomie, Bull. et mém. Soc. de chir. de Paris **22**:565, 1896.

19. Bardenheurer, cited by Moore, C. A.: A Case of Cholecystogastrostomy, Brit. M. J. **1**:14, 1921.

20. Monod, M.: Suite de la discussion sur la cholédocotomie, Bull. et mém. Soc. de chir. de Paris **22**:546, 1896.

21. Jaboulay, M.: La cholécystogastrostomie pour les tumeurs de la tête du pancreas, Lyon méd. **89**:365, 1898.

22. Montognon and Duchamp: Obstruction néoplastique du cholédoque, abouchement de la vésicule dans l'estomac, Loire méd. **8**:142, 1899.

23. Perrin, F. H.: La cholécystogastrostomie dans l'occlusion supposée complète et directement irrémédiable du cholédoque, Thèse de Lyon, no. 96, 1902, p. 169.

24. Eichmeyer, W.: Beiträge zur Chirurgie des Choledochus und Hepaticus einschliesslich der Anastomosen zwischen Gallen-System und Intestinis, Arch. f. klin. Chir. **93**:857, 1910; **94**:1, 1911.

25. Kohr, H.: Die Praxis der Gallenwege-Chirurgie in Wort und Bild, Munich, J. F. Lehmann, 1913, vols. 1 and 2. Die gut- und bösartigen Neubildungen der Gallenblase und der Gallengänge unter besonderer Berücksichtigung eigener Erfahrungen, Ergebn. d. Chir. u. Orthop. **8**:471, 1914.

26. Jacobson, J. H.: Anastomosis of the Gallbladder to the Stomach: "Cholecystogastrostomy," Tr. Am. A. Obst. & Gynec. **27**:172, 1914.

(1914), Erdmann [27] (1918) and Barr [28] (1914) held the opinion that this operation produces better results than any other when there is a necessity for a biliary short circuit. Jacobson [26] and White [29] (1920) reported its successful use, with particular emphasis on the absence of ascending infection.

In recent years cholecystogastrostomy has been recommended for conditions other than obstruction of the common bile duct. After using it successfully in forty-seven cases, Babcock [30] (1920) advocated it for the control of hyperchlorhydria. In cases of small ulcers he anastomosed the gallbladder directly into the ulcerated areas instead of excising the ulcer or performing a gastro-enterostomy. Babcock [31] (1920-1921) and Heyd [32] (1921) expressed a preference for this operation rather than anastomosis at any point lower than the duodenum because in the case of anastomosis at a higher level there remains the possibility of reabsorption of the bile. Deaver [33] (1925) also favored the operation for this reason. Frenkel [34] found that a decrease of total acidity, especially free hydrochloric acid, was a constant result in his twenty-one patients with ulcers of the stomach and duodenum whom he treated by cholecystogastrostomy and cholecystoduodenostomy. Nazarov [35] (1927) obtained satisfactory results with cholecystogastrostomy in cases of ulcer of the stomach. He observed in four cases in which he had to do a secondary laparotomy that the symptoms of ulcer recurred coincident with constriction of the stoma; he therefore concluded that when a cholecystogastrostomy is performed the stoma should be at least from 2 to 3 cm. in diameter. (Wangensteen [36] [1928] stated the belief that in operations for obstruction of the common duct the chief cause

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27. Erdmann, J. F.: Obstructive (Malignant) Jaundice: Operative Relief by Cholecystogastrostomy, Ann. Surg. **67**:273 (March) 1918.

28. Barr, R. A.: "Cholecystogastrostomy," J. Tennessee M. A. **7**:454, 1914-1915.

29. White, C. S.: Cholecystogastrostomy, Surg., Gynec. & Obst. **31**:493, 1920.

30. Babcock, W. W.: Control of Hyperchlorhydria and Its Consequences by Cholecystogastrostomy, M. Rec. **98**:476 (Sept.) 1920.

31. Babcock, W. W.: Cholecystogastrostomy and Cholecystoduodenostomy, Am. J. Obst. & Gynec. **1**:854 (May) 1921.

32. Heyd, C. G.: Cholecystogastrostomy and the Courvoisier Gallbladder, J. A. M. A. **77**:339 (July 30) 1921.

33. Deaver, J. B.: Cholecystectomy: External and Internal Cholecystostomy, Ann. Surg. **81**:761, 1925.

34. Frenkel, A.: Der Einfluss der Cholecystogastrostomie auf den Magenchemismus beim Magen- und Duodenal-Ulcus, Zentralbl. f. Chir. **52**:1459, 1925.

35. Nazarov, N. N.: Cholecystogastrostomy for Gastric Ulcer, Surg., Gynec. & Obst. **45**:474, 1927.

36. Wangensteen, O. H.: Cholangeitis Following Cholecystenterostomy, Ann. Surg. **87**:54, 1928.

of complications is also a narrowing of the stoma.) Braithwaite [37] (1926) stated that in cases of an inaccessible gastric ulcer or an ulcer which is too far removed from the pyloric region to be bathed by regurgitated duodenal juice cholecystogastrostomy is the operation of choice, with a regulated dietary regimen. Thus he agreed with most investigators as to the rôle of bile in the stomach. DuBose [38] (1924) advocated cholecystogastrostomy even in cases of perforated gastric or duodenal ulcer, perforation of the gallbladder and obscure or chronic intermittent jaundice. He stated that the stoma will not close if it is properly made and if the common duct is ligated and divided. Parenthetically, it may be remarked that present knowledge of the portal and lymphatic connections of the organs of the upper part of the abdomen, as pointed out by Sweet,[39] Kodama [40] and others, suggest an important argument against cholecystogastrostomy as the treatment for peptic ulcer. If it is true that a low grade infection in an organ of the upper part of the abdomen may result in or continue a low grade infection in some other organ, then, although one may correct chemical abnormalities in the gastric content due to disturbance of pyloric function, one at the same time exposes the gallbladder to infection, if infection is not already present. The secondarily infected gallbladder may thus perpetuate the conditions that resulted in the original ulcer for which treatment was instituted. These are theoretical considerations, but they must be weighed in accepting the evidence brought forward earlier.

Although the employment of cholecystogastrostomy in the treatment of ulcer is an interesting development, the place of this operation has been almost entirely in the treatment of obstruction of the common bile duct. The clinical literature on this phase is large and need not be reviewed with any completeness. DuBose,[38] White,[29] Heyd,[32] Villard and Richer,[41] Beaver,[6] Erdemann and Heyd,[42] Babcock,[30] Muller,[43]

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37. Braithwaite, L. R.: Surgical Treatment of Chronic Duodenal and Gastric Ulcer: Cholecystogastrostomy as the Operation for Inaccessible Gastric Ulcer, Lancet **1**:900, 1926.

38. DuBose, F. G.: Cholecystogastrostomy and Cholecystoduodenostomy, Surg., Gynec. & Obst. **39**:295, 1924; Cholecystogastrostomy, South. M. J. **22**:674, 1927.

39. Sweet, J. E., and Deaver, J. B.: Prepancreatic and Peripancreatic Disease with a Consideration of the Anatomic Basis of Infection from the Gall Bladder to the Pancreas, J. A. M. A. **77**:194 (July 16) 1921.

40. Kodama, S.: The Lymphatics of the Extrahepatic Biliary Passages, Surg., Gynec. & Obst. **43**:140, 1926.

41. Villard, E., and Richer: Le cholecysto-gastrostomie, Rev. de chir., Paris **63**:455, 1925.

42. Erdemann, J. F., and Heyd, C. G.: Relief of Chronic Obstructive Jaundice by Palliative Operation, Am. J. M. Sc. **152**:174, 1916.

43. Muller, G. P.: Cholecyst-Duodenostomy, Ann. Surg. **84**:95, 1926.

Walters,[44] Mayo,[45] Moore,[46] Ralphs,[47] Downes,[48] Stretton,[49] McNealy,[50] Murdy [51] and Weinberg, Wallin and Binger [15] reported favorable clinical experiences. The types of lesion for which these operations have been performed include carcinoma of the head of the pancreas, carcinoma of the common duct and the papilla of Vater, chronic pancreatitis with obstruction and obstruction due to anomalies and stricture. Many of these authors emphasized the ease of technical performance, the lack of digestive disturbance and the low mortality. Horsley,[14] on the other hand, reserved cholecystogastrostomy for use as a last resort.

The rationale of cholecystogastrostomy in this connection hardly needs comment. The relief of progressive obstructive jaundice associated with these conditions is of itself a desideratum. The operation prevents progressive hepatic damage from back pressure with an early onset of so-called cholemia. It removes the distressing itching of the jaundiced patient and ordinarily improves the appetite and produces a sense of well-being. It may convert a bedridden, emaciated, somnolent or otherwise distressed person into one who may go about and attend to his affairs. In cases of a disease which in itself is not destructive, such as chronic pancreatitis, a clinical cure may result. In cases of malignant disease the operation is only palliative. In the latter type of case, in which the patient often presents a poor risk, the technical simplicity of the operation recommends it. In cases of stricture of the common bile duct the gallbladder is rarely available because of previous inflammation. If it is available, this operation is to be preferred to hepaticoduodenostomy or implantation of an external fistula because of its relatively low mortality and its simplicity.

In addition to the uses already mentioned, DuBose [38] proposed the employment of cholecystogastrostomy instead of cholecystectomy or cholecystostomy in cases of cholecystitis or cholangeitis not due to calculi. This proposition has not been at all widely approved, as it carries with it the fundamental disadvantage that makes cholecystostomy undesirable in the treatment of these conditions, namely, the saving of the

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44. Walters, W.: Cholecystogastrostomy, Surg., Gynec. & Obst. **42**:825, 1926.

45. Mayo, C. H.: Jaundice and Its Surgical Significance, Surg., Gynec. & Obst. **30**:545, 1920.

46. Moore, C. A.: A Case of Cholecystogastrostomy, Brit. M. J. **2**:826, 1921.

47. Ralphs, G.: The Operation of Cholecystogastrostomy, Brit. M. J. **1**:14, 1922.

48. Downes, W. A.: Chronic Obstructive Jaundice: A Report of Nine Cases Treated by Cholecystogastrostomy, Tr. South. S. **35**:342, 1922.

49. Stretton, J. L.: Cholecystogastrostomy, Brit. M. J. **2**:600, 1922.

50. McNealy, R. W.: Operative Case: Obstructive Jaundice, Journal-Lancet **43**:636 (Dec. 15) 1923.

51. Murdy, R. L.: Indications for Cholecystenterostomy, Journal-Lancet **43**: 89 (Feb. 15) 1923.

gallbladder, in the wall of which infection lurks. The same may be said of DuBose's [39] proposal to employ cholecystogastrostomy in the treatment of more acute conditions, such as perforation of the gallbladder. In confirmation of these objections one may refer to Deaver's [38] statements that an infected gallbladder never entirely recovers pathologically and bacteriologically, and that a gallbladder that recovers from infection and one that has been the seat of stones invite further infection and the formation of more stones. Illingsworth [52] found bacteria in the walls of gallbladders even in cases in which the bile was found to be sterile. The successful use of this operation in such conditions is not recorded in the literature except by DuBose.[38]

On the basis of evidence, both clinical and experimental, brought forward in the literature and of theoretical considerations already presented, it seems obvious that the present value of cholecystogastrostomy is in the treatment of obstructions of the common duct by the lesions mentioned. This operation should take the place of cholecystostomy only in this type of disease and not in the acute type of disease of the gallbladder for which cholecystostomy is now occasionally performed. It does not seem probable that future experience will suggest its use instead of cholecystectomy for cholecystitis of any type. It must be considered that, in spite of the theoretical disadvantages outlined, the use of cholecystogastrostomy in the treatment of peptic ulcer may be justified with further experience. In cases in which there is a choice of cholecystogastrostomy and external drainage, cholecystogastrostomy is usually to be preferred.

So far the discussion has been limited to questions concerning the value of the method in obstruction of the common duct, irrespective of possible disadvantages. It is obvious that a gallbladder that is the seat of acute cholecystitis, gangrene, hydrops, thickening and contraction or a malignant condition is not suitable for the operation. In the entirely favorable case the question of what physiologic and pathologic disturbances may follow has not yet been settled. All of the evidence so far points to the fact that the gastric function is not disturbed by the discharge of bile into the lumen of the stomach. It is even suggested that a disturbance of gastric function may be corrected in this manner. The point at issue is rather whether or not hepatitis and cholangeitis can occur with such frequency and severity as to be a major disadvantage in the use of the operation. The purpose of the present paper is to throw light on this particular phase of the problem.

With the exception of the study of Weinberg, Wallin and Binger [18] and that of Gage [53] (1931), in which there was observed only a slight

52. Illingsworth, C. F. W.: Types of Gallbladder Infection; Study of One Hundred Operated Cases, Brit. J. Surg. **15**:221, 1927.

53. Gage, I. M.: Changes in the Liver Following Cholecystogastrostomy and Cholecystoduodenostomy, Proc. Soc. Exper. Biol. & Med. **28**:693, 1931.

to moderate increase in pathologic findings over the corresponding normal livers, all of the experimental attacks on this problem have shown a tremendous degree of hepatic infection as a result of the operation. In every case dogs were employed. These animals, of course, have a rich bacterial flora in the stomach which is not present in the human stomach. This renders comparison between the dog and the human being fallacious. Although Weinberg, Wallin and Binger [15] obtained the same results in the dog, they found that in a single monkey hepatic infection did not occur. They made no reference, however, to the bacteriologic characteristics of the monkey's stomach.

The clinical literature on cholecystogastrostomy is marked by the fear of this complication. Whether this state of mind has arisen from the aforementioned experimental evidence or whether it has come from actual clinical experience with the occurrence of hepatitis and cholangeitis following cholecystogastrostomy is not clear from a reading of the literature. One fact stands out. Although the majority of authors mention the danger, there is a striking paucity of reports showing the incidence of the complication. Nazarov [35] performed secondary laparotomy in four cases in which he had previously performed cholecystogastrostomy for gastric ulcers, but in his report he did not mention the condition of the liver. All of these reoperations were performed for the recurrence of symptoms of ulcer. In the reports of five cases in which he performed a secondary operation, from eight months to five and one-half years after cholecystogastrostomy, Steel [54] stated that the livers were normal to palpation and inspection. No microscopic sections were made. All of Steel's cholecystogastrostomies were performed for obstruction of the common duct. The secondary laparotomies were performed for the recurrence of symptoms, acute appendicitis, pyloric obstruction, incarcerated hernia and epigastric distress. DuBose [38] did not make a microscopic study of the liver in the case in which he performed an operation secondary to cholecystogastrostomy. A thorough search of the literature has not revealed one report of a case in which the presence of hepatitis or cholangeitis following cholecystogastrostomy was definitely substantiated by a microscopicopathologic study of sections of the liver removed at operation or at necropsy. It is still more amazing that no cases have been found in which there was a presumptive clinical diagnosis of these sequelae.

In making this statement it is well to differentiate between cholecystogastrostomy and cholecystenterostomy, a distinction which some authors do not clearly make. There are some references to clinical cases of hepatic infection following the latter operation. For example,

54. Steel, W. A.: Internal Drainage of Gallbladder as a Routine Operative Procedure, Surg., Gynec. & Obst. **44**:393, 1927.

Wangensteen [36] cited two cases reported by Kausch [55] in which cholecystojejunostomy was performed for obstructive jaundice and carcinoma of the head of the pancreas. In each of these cases at necropsy suppurative cholangeitis was revealed as the cause of death. Gatewood and Lawton [56] reported a case of clinical infection in which at autopsy cholangeitis, hepatitis and cirrhosis were found, but they did not state what type of operation was performed.

Except for the mention by Strauss in a discussion of Judd's [57] paper read before the American Medical Association, no reference has been made in the reports of these cases of infection of the biliary tract to the possible presence of the infection before the operation was performed. However, it is safer in this discussion to assume that such infection is the result of operation rather than to attempt to explain it on the basis of a preexisting infection. Yet in any single instance one cannot say that previously present infection may not have been responsible.

It is not wise to assume from this evidence, even if all of the reports had been uncovered in this search of the literature, that cholecystogastrostomy has not been incriminated. On the other hand, in relation to the number of operations of all types which have been performed, the incidence of hepatic infection in the cases reported is unquestionably low. Judd [57] said that "infection is not as apparent clinically as might be expected from a study of gallbladders and livers of experimental animals after the operation." In turn Wangensteen [36] said: "The complication of cholangeitis in patients following cholecystenterostomy has only infrequently been observed. Those who have had a considerable experience with the method uniformly agree that the danger of subsequent infection is slight." To judge from the literature, Wangensteen's second sentence is not entirely justified in that a majority of authors refer to infection as a disadvantage to the operation. One wonders, therefore, whether this generally felt fear may not be another of those curious medical traditions that live from textbook to textbook with little justification for their origin.

The present series of experiments was based on an attempt to perform cholecystogastrostomy under conditions in experimental animals simulating those in the human being and thus to obtain results which can be used comparatively with greater safety. The crux of the experimental method was the performance of the operation by the anastomosis

55. Kausch, W.: Ueber Gallenweg-Darmverbindungen, Arch. f. klin. Chir. **97**:574, 1912.

56. Gatewood and Lawton, S. E.: The Effect of Cholecystenterostomy on the Biliary Tract, Surg., Gynec. & Obst. **1**:40 (Jan.) 1930.

57. Judd, E. S.: "Sidetracking" Operations in Obstructive Jaundice, J. A. M. A. **91**:300 (Aug. 4) 1928.

of the dog's gallbladder with its stomach after rendering the stomach relatively free from bacteria. This was accomplished, in brief, by creating a gastric pouch separated from the food current for a considerable time before the anastomosis, as will be detailed later (fig. 1). After the initiation of these experiments it was found that the same principle had been suggested and employed clinically by Monprofit [58] Kausch [55] and Cholin.[59] These operations were in general cholecystojejunostomies performed in a manner resembling Roux's gastroenterostomy in Y.

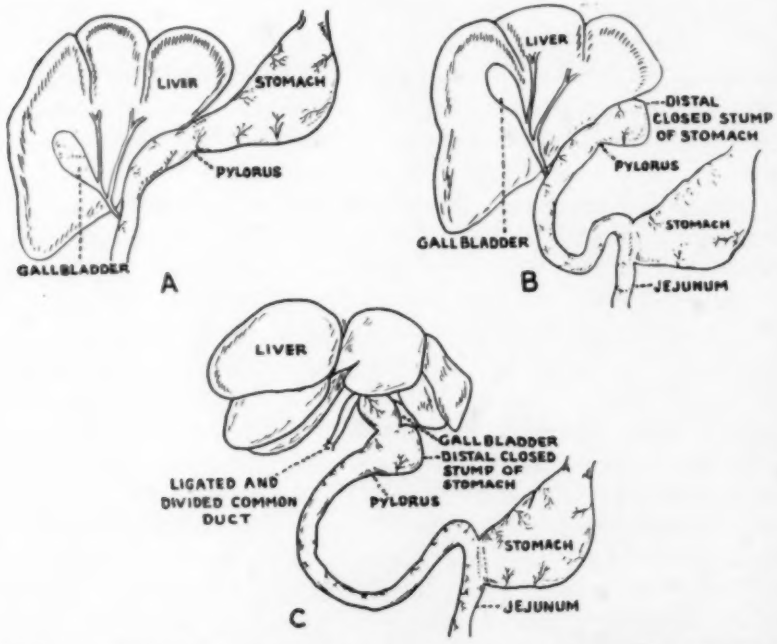

Fig. 1.—Sketches of the operative procedures: *A*, the normal relationships in the dog; *B*, the first stage operation of gastric division and gastrojejunostomy, showing the formation of the gastric pouch, and *C*, the second stage operation of cholecystogastrostomy, the previously prepared gastric pouch being used.

METHOD

In the following experiments forty dogs were used without selection as to weight, sex or breed. The dogs were fed the routine laboratory maintenance diet, which consisted of purina chow, meat scraps and oatmeal mash. Food was withheld from the animals for twelve hours before each operation. For thirty-two dogs the anesthetic used was sodium amytal, 0.05 Gm. per kilogram of body

58. Monprofit, A.: On Cholecystenterostomy in the Form of a "Y," Brit. M. J. **2**:991, 1908.

59. Cholin, N. K.: Zur Tecknik der Cholecystoenterostomie, abstr., Zentralbl f. chir. **36**:1769, 1909.

weight in a 10 per cent solution. This was administered in all instances intraperitoneally. In all except a few animals the anesthesia was satisfactory. In three of the thirty-two animals ether was necessary to secure proper relaxation. Three animals failed to recover from the anesthesia. Death was attributed to a possible error in the dosage. Eight dogs were given only ether.

All of the following operative procedures were performed under strictly aseptic precautions. The clean-shaven abdomen of the animal was washed with soap and water and then with iodine, 3 per cent, and alcohol, 95 per cent, as a preparation of the operative field. The abdominal closure was effected in all instances as follows: Linen thread was used for the peritoneum, no. 1 chromic catgut for the fascia, and linen thread for the skin.

The procedures may be divided into two groups: control and experimental. In the control groups the effects on the liver of all of the elements in the experimental operations were studied by the performance of each operation separately in different animals. The results of the control part of the study have proved extremely interesting in themselves and present certain evidence throwing light on the general subject of infections of the upper part of the abdomen.

CONTROL STUDIES

The several control procedures, with the results obtained, were as follows:

Ligation and Division of the Common Bile Duct.—The abdomen was entered through a high midline incision. The common bile duct was dissected free and ligated in three places with no. 1 chromic catgut, about 1 cm. proximal to the point at which it enters the duodenum. Care was taken that the ligatures were below the entrance of the left hepatic duct. The duct was then divided between the two distal ligatures so that the proximal stump would be doubly ligated. The abdomen was closed in layers.

Three dogs were used. The animals showed clinical evidence of jaundice and died from the tenth to the thirteenth day after operation from bile peritonitis, resulting from rupture of the common bile duct or of the gallbladder. In dog 60 exploration was made on the thirteenth postoperative day, and a distended, grayish gallbladder containing 125 cc. of dark green, viscid bile was found. The liver in each animal was enlarged and deeply bile-stained. Microscopically, the liver showed jaundice with marked acute hepatitis and degeneration of the hepatic cells.

Simple Cholecystogastrostomy.—The abdomen was opened by means of a high midline incision. The gallbladder was aspirated of its bile, of which a culture was made. The gastrohepatic ligament was ligated and divided carefully so as to allow the stomach to be pulled up. The gallbladder was anastomosed to the stomach in the distal third region, from 3 to 4 cm. above the pyloric ring near the lesser curvature. The suture method of anastomosis was employed, two rows of no. 00 chromic catgut or, in a few instances, fine silk being used. No clamps were used. An attempt was made to have a resultant stoma of from 1

to 2 cm. in diameter. A small section of liver was removed for culture, and a microscopic examination was made whenever a cholecystogastrostomy was performed. The abdomen was then closed.

Three dogs were used. Exploration was made at various periods after operation, from the eighty-sixth to the one hundred and eighty-ninth day. In each animal the liver and gallbladder revealed gross pathologic changes. The stoma was patent, and the common duct was somewhat dilated. No particles of food were found in the gallbladder. Microscopic examination of the liver showed a slight infiltration with round cells throughout, with some fibrosis about the portal system and central veins.

Combination of Cholecystogastrostomy and Ligation and Division of the Common Duct.—Cholecystogastrostomy and ligation and division of the common duct were performed on three dogs after the technic described earlier. Exploration was made on the twelfth and the two hundred and eighth day after operation. On each animal the gallbladder was gray and somewhat dilated, as was the common duct. The stoma was patent. The liver macroscopically showed signs of fibrosis. Microscopic study of the liver revealed marked acute hepatitis, acute and chronic cholangeitis and slight portal cirrhosis. These findings simply repeat the observations of Gatewood and Poppens,[12] Lehman,[13] Horsley [14] and others. They represent experimental results on which the idea of the importance of hepatic infections following cholecystogastrostomy has been founded.

Gastric Division with a Polya-Balfour Anastomosis.—The abdomen was opened by means of a high midline incision. The gastric vessels and the greater and lesser omentum were ligated and divided in the region of the distal third of the stomach. The stomach was then cut across between rubber-covered clamps. The distal third of the stomach was closed with two rows of no. 00 chromic catgut. The proximal portion of the stomach was anastomosed to the jejunum from 10 to 15 cm. from the duodenum, the Polya-Balfour technic being used. Two rows of no. 00 chromic catgut or fine silk were used. The abdomen was then closed (fig. 1 *B*).

Twenty-five dogs were used. Exploration was made between the fourteenth and the ninety-fourth day after operation. In each animal the gallbladder appeared to be normal, and an average of 33 cc. of bile was aspirated. Cultures of the bile showed Staphylococcus albus or Bacillus coli-communis. Negative cultures were obtained in 40 per cent. The liver appeared to be normal. Cultures of the liver revealed no organisms in 45 per cent of the dogs. The organism in the remaining cultures were Staph. albus, B. coli and, in one instance, Streptococcus haemolyticus. In cultures from the lumen of the closed distal stump Staph. albus and Staphylococcus aureus were most frequently found. B. coli-communis was also frequently recovered, as was Bacillus

aerogenes. Two cultures revealed bacilli of the Salmonella group, and two revealed no organisms. Microscopic examination of the liver showed in every instance a slight to marked infiltration with round cells and polymorphonuclears and fibrosis (figs. 2 and 3). These changes were most marked in the region of the central veins and portal system. In almost every liver there was fatty degeneration of the parenchyma, and the hepatic lobules were not distinct.

Cholecystostomy.—The abdomen was entered through a high midline incision. The gallbladder was exposed, and the bile was aspirated.

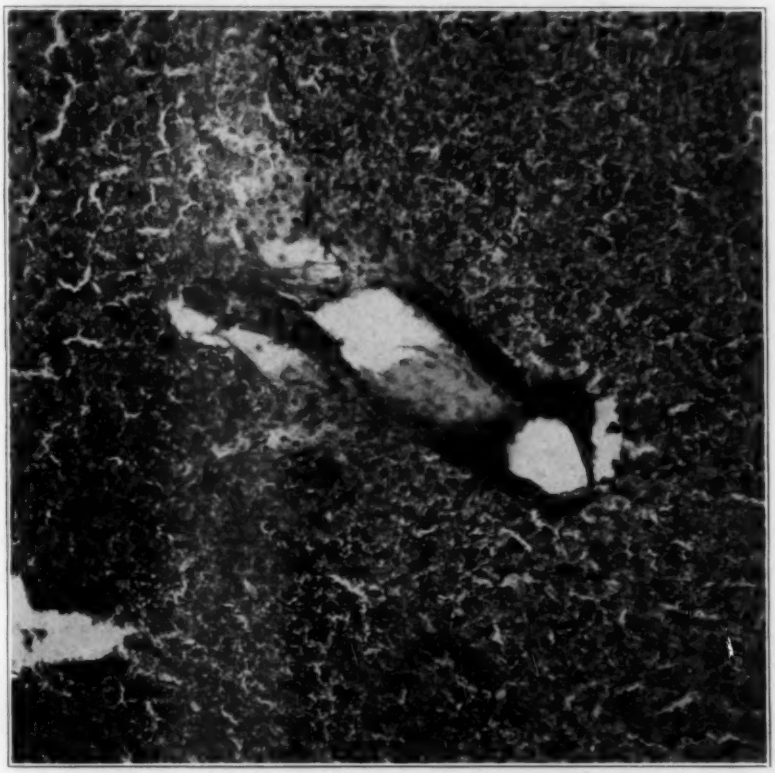

Fig. 2.—Low power photomicrograph of a section of the liver removed from dog 33 three months following gastric division and gastrojejunostomy (fig. 1 *B*). Note the cellular infiltration and the increase in the fibrous tissue.

The fundus of the gallbladder was then grasped, and an opening large enough to admit a small rubber tube was made. A purse-string suture was put in around the tubing, which was transfixed by the suture. The purse-string suture was drawn tight as the tubing was pushed in. A second row of no. 00 chromic catgut was then placed. The gallbladder was anchored to the peritoneum by two interrupted catgut sutures. The tube was brought to the outside, and the abdomen was closed.

Two dogs were used. The animals seemed to go down-hill fast, losing weight rapidly and showing a decrease in appetite. The bile decreased in flow until on the seventeenth postoperative day there was little greenish-yellow bile flowing from the cholecystostomy tube. Exploration revealed that the gallbladder was very much shrunken and surrounded by grayish fibrous tissue. The liver showed gross pathologic change, especially in the region closest to the gallbladder. Microscopic sections of the liver revealed acute hepatitis with fatty degeneration of

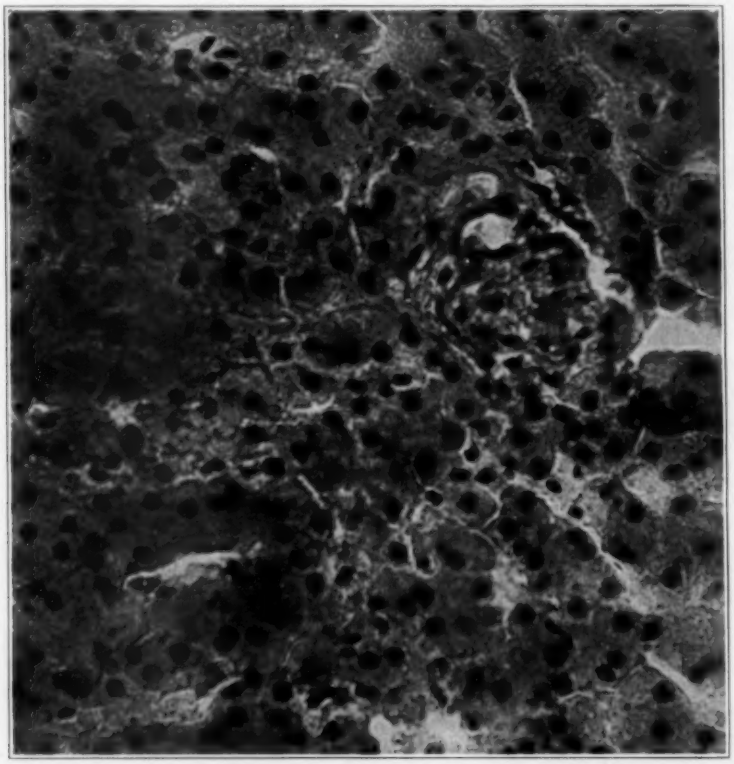

Fig. 3.—High power photomicrograph of the section shown in fig. 2.

the parenchyma. The infiltration with polymorphonuclears and round cells was most marked in the vicinity of the portal systems.

Cholecystogastrostomy—Modified Technic.—This method was an unsuccessful attempt to perform cholecystogastrostomy on the principle of the ureteral transplantation recently reported by Coffey.[60] It has no direct bearing on the experiments to follow.

60. Coffey, R. C.: Production of Aseptic Uretero-Enterostomy by Suture Transfixing Ureteral Wall and Intestinal Mucosa, J. A. M. A. **94**:1748 (May 31) 1930.

The abdomen was opened through a high midline incision. The gastrohepatic ligament was ligated and divided, and the stomach brought forward. An incision of about 3 inches (7.6 cm.) in length, which cut through the serosal and muscular coats, was made in the distal anterior third of the stomach. The gallbladder was pulled downward by means of a suture transfixing the serosal layer in the region of the fundus. The gallbladder was anchored to the stomach by means of this suture. A silk suture was taken between the stomach and the gallbladder, penetrating into the lumen of each. This suture was tied tight. The gallbladder was embedded in the wall of the stomach by suturing the muscular and serosal layers over it. The common bile duct was then dissected free and ligated as previously described. The abdomen was closed.

Four dogs were used. Exploration was made on from the seventeenth to the twenty-sixth day after operation. In no instance when the stomach was opened, was a stoma observed between the gallbladder and the stomach. The gallbladders of these dogs were markedly distended; they were dark green but free from adhesions. Macroscopically and microscopically, the livers revealed the pathologic pictures seen in cases of simple ligation and division of the common duct. One interesting fact was noted. In each dog the portion of the gallbladder embedded in the wall of the stomach had shrunk until it resembled a tube. The gastric mucosa over this region was slightly thickened.

In general, the results of the control procedures bring out the fact that all of the operations performed resulted in inflammatory changes in the liver. The changes followed not only the operations on the biliary tract but those limited to the stomach and the jejunum. The presence of this hepatitis will be further emphasized in the discussion of the results of the experimental procedures.

In addition, the occurrence of hepatitis following an operation on the stomach presents striking experimental evidence confirming the intimate pathologic association of the liver with the digestive tract. Graham [61] found similar hepatitis in three cases of appendicitis; its occurrence with cholecystitis is universal. Although again one must be cautious in comparing the dog with the human being, there arises the question as to whether inflammatory disease of the stomach and operations on the stomach in the human being may not result as constantly in hepatitis as cholecystitis has been shown to. A series of biopsies made on specimens of liver following gastric resection for noninflammatory disease of the stomach such as carcinoma would be interesting. This would be difficult to obtain because of the rarity of secondary

61. Graham, E. A.: Diseases of the Gall Bladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928, p. 122.

Observations on Twenty-Five Animals on Which Cholecystogastrostomy and Ligation and Division of the Common Duct Were Performed

Dog	Date of Polya-Balfour Operation	Interval to Cholecystogastrostomy, Days	Interval to Exploratory Operation or Death, Days	Cultures				Microscopicopathologic Changes in Liver			Date and Causes of Death
				Second Operation			Third Operation: Liver	Second Operation	Third Operation	Post Mortem	
				Stump of Stomach	Bile	Liver					
19	7/30/30	98	9[a]	Salmonella group	Negative	Negative	Negative	Slight infiltration with round cells and polymorphonuclears; fibrosis about the portal system	.....	Slight infiltration with round cells and polymorphonuclears; fibrosis	11/13/30: Bile peritonitis; rupture of gallbladder
28	10/17/30	32	92	Staph. aureus	Negative	Negative	B. Welchii	Occasional infiltration with round cells and polymorphonuclears; fibrosis about the portal system	Occasional infiltration with round cells and polymorphonuclears; fibrosis	Slight infiltration with round cells and polymorphonuclears; fibrosis	4/23/31: Acute dilatation of stomach
30	8/11/30	87	95	Staph. albus	Staph. albus	Negative	Negative	Slight infiltration with round cells about the central veins; cloudy swelling	Slight infiltration with round cells and polymorphonuclears; fibrosis	Marked infiltration with round cells and polymorphonuclears; hemorrhage	3/10/31: Perforated jejunal ulcer; peritonitis
33	8/12/30	94	94	B. coli	Hay bacillus	Negative	Negative	Slight infiltration with round cells and polymorphonuclears; fatty degeneration	Slight infiltration with round cells and polymorphonuclears	Infiltration with round cells and polymorphonuclears; hemorrhage	10/14/31: Acute pancreatitis
38	10/28/30	21	92	B. coli; Staph. albus	Negative	Staph. albus	Staph. albus	Slight infiltration with round cells and polymorphonuclears; slight fibrosis; fatty degeneration	Slight infiltration with round cells and polymorphonuclears; fibrosis	Infiltration with round cells and polymorphonuclears; fatty degeneration; fibrosis	9/8/31: Acute inanition
40	11/20/30	20	71	Negative	Staph. albus	Staph. albus	B. coli; B. proteus	Slight infiltration with round cells and polymorphonuclears; slight fibrosis; fatty degeneration	Slight infiltration with round cells and polymorphonuclears	Marked infiltration with round cells and polymorphonuclears	2/19/31: Intestinal obstruction; intussusception
41	11/25/30	15	90	B. coli; Staph. albus	Staph. albus	Staph. albus	B. coli	Infiltration with round cells and polymorphonuclears; fibrosis throughout	Slight infiltration with round cells and polymorphonuclears; fibrosis	Marked infiltration with round cells and polymorphonuclears; fibrosis	3/11/31: Anesthesia

43	10/28/30	23	32*	B. coli; Salmonella group	Negative	Staph. albus	.....	Slight infiltration with round cells and polymorphonuclears; fibrosis; cloudy swelling	.....	Slight infiltration with round cells and polymorphonuclears; fibrosis; cloudy swelling	12/22/30: Perforated jejunal ulcer; peritonitis
46	1/ 6/31	23	19*	Negative	Negative	Negative	B. coli	Slight infiltration with round cells and polymorphonuclears; fibrosis	.....	Slight infiltration with round cells and polymorphonuclears	2/17/31: Perforated jejunal ulcer; peritonitis
47	10/31/30	14	94	B. coli	Staph. albus	Staph. albus	Str. non-haemolyticus	Slight infiltration with round cells	Slight infiltration with round cells	Infiltration with round cells and polymorphonuclears; cloudy swelling	9/29/31: Autopsy revealed no cause of death
49	11/13/30	25	85*	B. coli; Staph. albus	Staph. albus	Staph. albus	Negative	Slight infiltration with round cells and polymorphonuclears; fibrosis; fatty degeneration	.....	Pathologic picture obscured by post-mortem change	3/3/31: Perforated jejunal ulcer; peritonitis
51	1/ 6/31	23	48	Staph. albus	Staph. albus	Staph. albus	Str. non-haemolyticus	Infiltration with round cells; fibrosis	Slight infiltration with round cells; fibrosis	Infiltration with round cells and polymorphonuclears; fibrosis; cloudy swelling	4/10/32: Acute inanition
56	1/ 8/31	22	3*	B. coli	B. coli; Staph. albus	B. coli; Staph. albus	Negative	Slight infiltration with round cells and polymorphonuclears; fibrosis; fatty degeneration	.....	Slight infiltration with round cells; fibrosis; fatty degeneration	2/2/31: Intestinal obstruction due to adhesions
57	1/13/31	21	21*	Negative	Negative	Negative	B. coli	Slight infiltration with round cells; fibrosis; fatty degeneration; cloudy swelling	....	Slight infiltration with round cells; fibrosis; fatty degeneration	2/24/31: Intestinal obstruction due to adhesions
63	1/14/31	23	13*	B. coli	B. coli	B. coli	B. coli	Infiltration with round cells and polymorphonuclears; fibrosis	.....	Pathologic picture obscured by post-mortem change	2/19/31: Bile peritonitis
64	1/14/31	23	40	B. coli; Staph. albus	Negative	Negative	Staph. albus	Infiltration with round cells and polymorphonuclears; fibrosis	Slight infiltration with round cells and polymorphonuclears	Infiltration with round cells and polymorphonuclears; cloudy swelling	6/13/31: Intestinal obstruction; intussusception
65	1/16/31	24	0*	Staph. albus	Negative	Negative	.....	Infiltration with round cells	.....	Infiltration with round cells	2/9/31: Anesthesia

* Death

Observations on Twenty-Five Animals on Which Cholecystogastrostomy and Ligation and Division of the Common Duct Were Performed—Continued

Dog	Date of Polya-Balfour Operation	Interval to Cholecystogastrostomy, Days	Interval to Exploratory Operation or Death, Days	Cultures				Microscopicopathologic Changes in Liver			Date and Causes of Death
				Second Operation			Third Operation: Liver	Second Operation	Third Operation	Post Mortem	
				Stump of Stomach	Bile	Liver					
171	9/ 4/33	35	2*	Staph. albus	B. coli	Anaerobic bacillus; Staph. albus	Anaerobic bacillus	Infiltration with round cells and polymorphonuclears; fibrosis; cloudy swelling	.....	Slight infiltration with round cells and polymorphonuclears; fibrosis	10/11/31: Acute inanition
172	9/ 4/33	35	93	Str. nonhaemolyticus; B. coli	B. coli	B. coli; Str. nonhaemolyticus; anaerobic bacillus	B. coli; B. aerogenes; anaerobic bacillus	Infiltration with round cells and polymorphonuclears; fatty degeneration	Slight infiltration with round cells and polymorphonuclears	Slight infiltration with round cells and polymorphonuclears; moderate fibrosis	1/17/34: Perforated jejunal ulcer; peritonitis
173	9/ 4/33	35	76	B. coli; hay bacillus	B. proteus	B. coli; hay bacillus	B. coli	Infiltration with round cells and polymorphonuclears; fatty degeneration	Slight infiltration with round cells and polymorphonuclears	Moderate infiltration with round cells and polymorphonuclears; moderate fibrosis	12/25/33: Acute dilatation of stomach
174	9/ 4/33	35	93	B. coli; hay bacillus	B. coli; B. aerogenes	Negative	B. coli; B. aerogenes; B. proteus	Slight infiltration with round cells and polymorphonuclears; cloudy swelling	Slight infiltration with round cells and polymorphonuclears; cloudy swelling		
176	9/ 4/33	35	33*	B. coli; hay bacillus	Negative	Staph. albus	B. aerogenes	Infiltration with round cells and polymorphonuclears throughout; fatty degeneration	.....	Marked infiltration with round cells and polymorphonuclears; cloudy swelling	11/11/33: Intestinal obstruction at ileocecal valve
181	10/ 9/33	38	48*	B. coli; B. aerogenes	Negative	Staph. albus; gram-negative bacilli	Staph. albus; anaerobic bacillus	Infiltration with round cells and polymorphonuclears; fibrosis	.....	Marked infiltration with round cells and polymorphonuclears; hemorrhagic areas	1/4/34: Perforated jejunal ulcer; peritonitis
182	10/ 9/33	38	4*	B. coli; B. proteus; B. aerogenes	Negative	Anaerobic bacillus; gram-negative bacillus	B. aerogenes	Infiltration with round cells and polymorphonuclears; cloudy swelling; fatty degeneration	.....	Marked infiltration with round cells and polymorphonuclears; moderate fibrosis	11/20/33: Abscesses of liver; gallbladder filled with blood
183	10/ 9/33	38	55	B. coli	Negative	Staph. albus; anaerobic bacillus	B. coli; B. aerogenes; anaerobic bacillus	Slight infiltration with round cells and polymorphonuclears; cloudy swelling	Slight infiltration with round cells and polymorphonuclears		

laparotomy under these circumstances. However, a series of biopsies on the liver in cases of peptic ulcer in which the gallbladder is normal would be easier to obtain and might throw light on this subject.

EXPERIMENTAL STUDIES

The results of bacteriologic study will be discussed in the following paragraphs.

First Stage Operations.—Twenty-five dogs were first subjected to gastric division with a Polya-Balfour anastomosis. These were the animals studied in the control group before the second stage procedure.

Second Stage Operations.—At varying intervals of from fourteen to ninety-four days (table) a cholecystogastrostomy, the closed distal stump of the stomach being employed, with ligation and division of the common duct was performed on each animal (fig. 1 *C*). It was hoped by these means to unite the lumen of the gallbladder with the lumen of the stomach after the latter had had time to free itself from bacteria. At this operation a biopsy specimen of the liver was obtained, and cultures were taken from the liver tissue, the bile and the mucosa of the closed gastric stump, as detailed in the description of the primary procedure. As will be remembered, in all except two instances, the pouch was not free from bacteria, but the contamination was relatively slight as compared with the normal stomach of the dog, both as to the number and particularly as to the variety of the organisms (fig. 4). At the time of the second stage most of the dogs showed a gain in weight or maintained the weight recorded at the time of the first operation.

It was planned to complete the study of the experimental animals by a third operation, at which exploration was to be carried out and a specimen from the liver obtained to observe the changes in the liver about three months after the second stage.

Of the original twenty-five dogs, twelve died before this exploratory laparotomy (dogs 19, 43, 46, 49, 56, 57, 63, 65, 171, 176, 181 and 182). Dog 65 died apparently of the anesthetic at the time of the second stage operation. Dogs 43, 46, 49 and 181 died of perforated jejunal ulcers thirty-two, nineteen, eighty-five and forty-eight days, respectively, following cholecystogastrostomy. Dog 63 died of bile peritonitis. Dog 171 died of acute inanition (no other cause of death was found). Dog 19 died nine days after cholecystogastrostomy of bile peritonitis due to rupture of the gallbladder. Dogs 56 and 57 died of intestinal obstruction resulting from adhesions three and twenty-one days, respectively, following cholecystogastrostomy. Dog 182 was the only one to die of hepatic infection. There were eleven deaths occurring at exploratory laparotomy. Dogs 30 and 172 died of perforated jejunal ulcers. Dogs 40 and 64 died of intussusception. Dogs 173 and 28 died of acute dilatation of the stomach. Dog 33 died of acute pancreatitis. Dogs 38

and 51 died of acute inanition. Dog 41 died of the anesthetic on the day following the exploratory laparotomy. At autopsy dog 47 revealed no obvious cause of death. Two dogs are still living.

Third Stage Operation.—Only thirteen dogs, therefore, were subjected to the third stage exploratory operation. A biopsy specimen of the liver was taken at intervals of from forty to ninety-five days following cholecystogastrostomy. In addition, the livers of dogs 43, 46 and

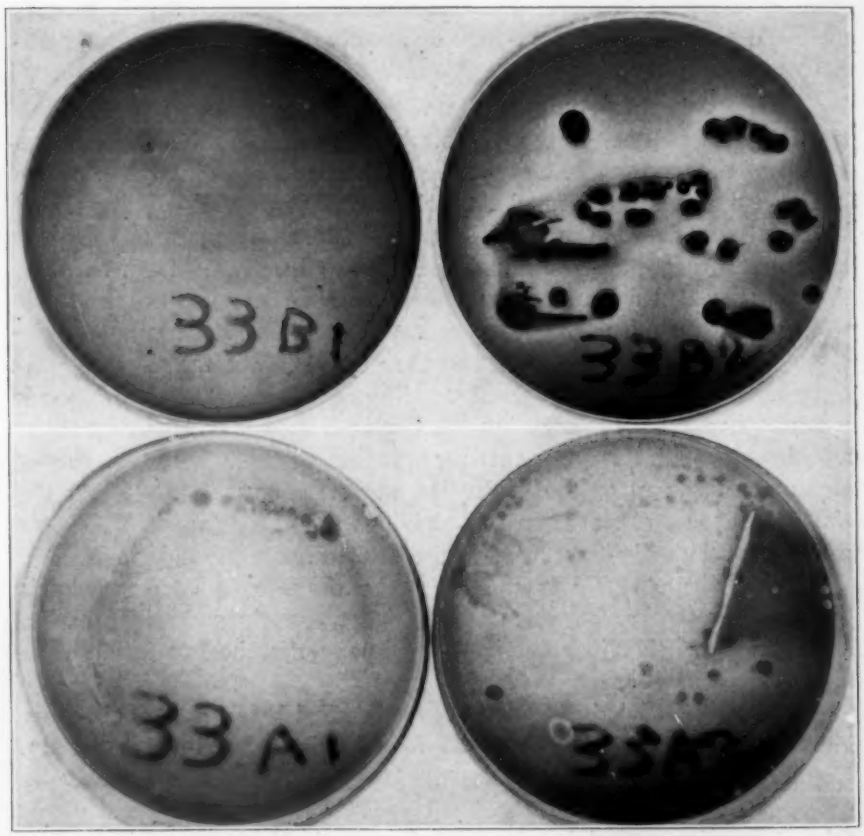

Fig. 4.—Photographs of plate cultures from the closed gastric pouch and functioning stomach of dog 33. Plates *B* are on Endo's medium; plates *A* are on blood agar. Plates *1* are from the closed pouch; plates *2* are from the functioning stomach. These plates demonstrate the absence of colon bacilli in the closed pouch and a relatively slight contamination with staphylococci as compared to the functioning stomach.

181, which died of perforated jejunal ulcers, were obtained before postmortem changes disturbed the pathologic picture, as were the livers of dog 19, which died of bile peritonitis, dogs 56, 57 and 176, which died of intestinal obstruction, dog 171, which died of acute inanition, dog

65, which died of the anesthetic, and dog 182, which died of abscess of the liver. Thus a total of twenty-three dogs were available for study of the effects on the liver of the experimental procedure.

At the exploratory operations there were found remarkably few adhesions and no marked gross pathologic changes in the gallbladder and liver (fig. 5). The absence of gross cholecystitis was a uniformly striking finding in comparison with the marked cholecystitis found after the usual type of experimental cholecystogastrostomy. Microscopic studies of the livers revealed in most instances a slight infiltration with polymorphonuclears and round cells and slight fibrosis, especially about

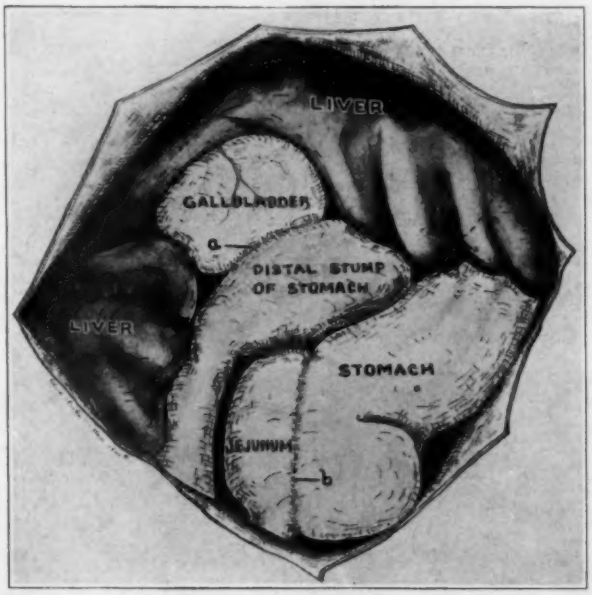

Fig. 5.—Drawing of the liver and the anastomosis as seen at exploratory operation three months after the second stage operation; *A*, cholecystogastrostomy, and *B*, gastrojejunostomy.

the portal system and central veins (figs. 6 and 7). The hepatic lobules were not distinct, and there was an absence of fatty degeneration. These changes seemed to be slightly more marked in the sections from the right lobes of the liver than in those from the left lobes. These sections, when compared with sections from the same livers removed at intervals following the first stage Polya-Balfour anastomosis, showed no more—perhaps less—infiltration and fibrosis. This comparison must be strongly emphasized. A section of liver from dog 182 was the only one to show a frank hepatic infection with formation of abscesses. Cultures of the livers revealed B. coli-communis, Staph.

Fig. 6.—Low power photomicrograph of a section of the liver removed three months following the second stage operation. Compare with figure 2. No increase in the hepatitis is seen.

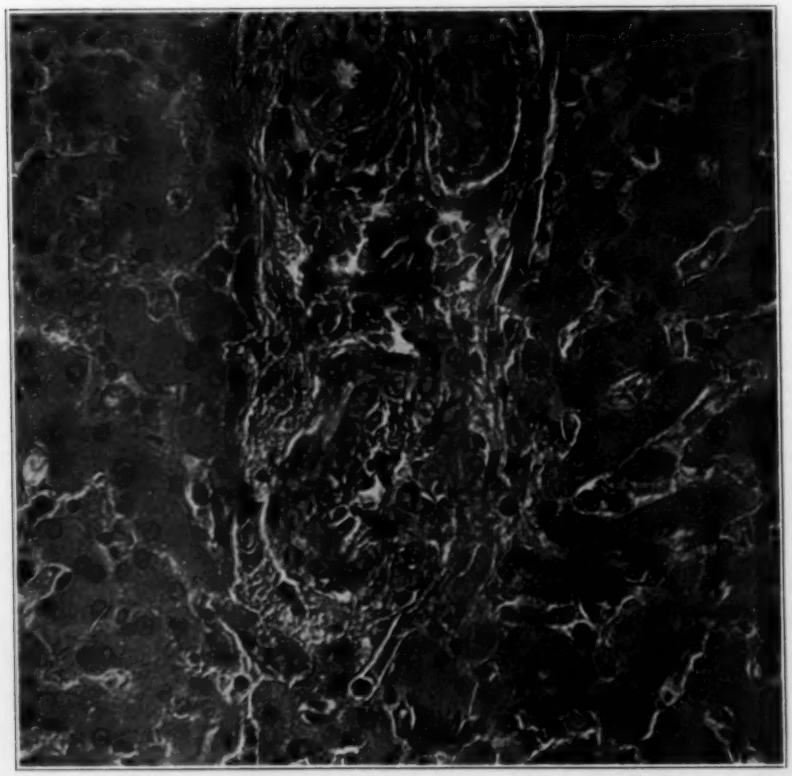

Fig. 7.—High power photomicrograph of the section of the liver shown in figure 6. Compare with figure 3.

Fig. 8.—Photograph of the stomach of a dog which died of perforation of a gastrojejunal ulcer. The site and appearance are entirely characteristic.

Fig. 9.—Photograph of the ulcer shown in figure 8, viewed from the lumen.

albus, Streptococcus nonhaemolyticus and Bacillus Welchii. Twenty-five per cent of the cultures revealed no organisms.

It is interesting that dogs 43 and 46, which died of peritonitis resulting from a ruptured ulcer before the exploratory operation, showed no more marked hepatitis than that found in the thirteen dogs from which specimens of liver were obtained at operation. On the other hand, the sections of liver obtained from dog 30 following death from perforation of a jejunal ulcer showed a much more acute picture of hepatitis than did sections of the same liver removed at operation ninety-five days previously. Furthermore, the livers of dog 19 (peritonitis) and dogs 56, 57 and 176 (obstruction), also obtained post mortem before exploratory laparotomy, showed no increase in hepatitis over that shown at the time of operation, respectively nine, three, twenty-one and thirty-three days previously.

The pathologic characteristics of the jejunal ulcers, from the perforation of which six animals died, is entirely similar to that of the so-called gastrojejunal ulcer found in man following gastrojejunostomy. The ulcers varied in number from one to four. They were invariably located in the jejunum opposite the open end of the stomach, toward which the food current is projected by gastric peristalsis (figs. 8 and 9).

COMMENT

At the initiation of this study it was assumed that the blind pouch of the dog's stomach would become relatively free from organisms and that an anastomosis with the gallbladder in this location would therefore more nearly simulate the conditions found in man. As has been shown earlier, the pouch still contains a considerable number of organisms even three months after isolation, although the number was fewer than that obtained in the normal dog's stomach. The truth of this assumption was tested by comparative cultures from the stomach and the closed pouch of the same animal (fig. 4). The importance of this deviation from the expected results becomes small in view of the other findings reported. It is also to be noted that bacteria were often recovered from the hepatic tissue and the bile in dogs that were apparently normal and on which no operation had been performed.

The striking fact is that thirteen dogs on which an exploratory operation was performed from one to three months after cholecystogastrostomy under the given conditions and ten dogs dying at shorter intervals after the same operation showed no increase of hepatic inflammation over that found at the time of a cholecystogastrostomy which followed an operation on the stomach. The degree of hepatitis found in three control animals in which simple cholecystogastrostomy with ligation and division of the common duct was performed according to

the usual experimental technic agrees materially with that reported by earlier experimenters. Of more importance is the fact that this degree of hepatitis is unmistakably greater than that found in the experimental animals. In other words, under one set of conditions, cholecystogastrostomy results in no augmentation of hepatitis already present, whereas under another set of conditions cholecystogastrostomy results in a marked development of hepatitis in a previously normal liver. These facts, of course, indicate clearly that the union of the gallbladder

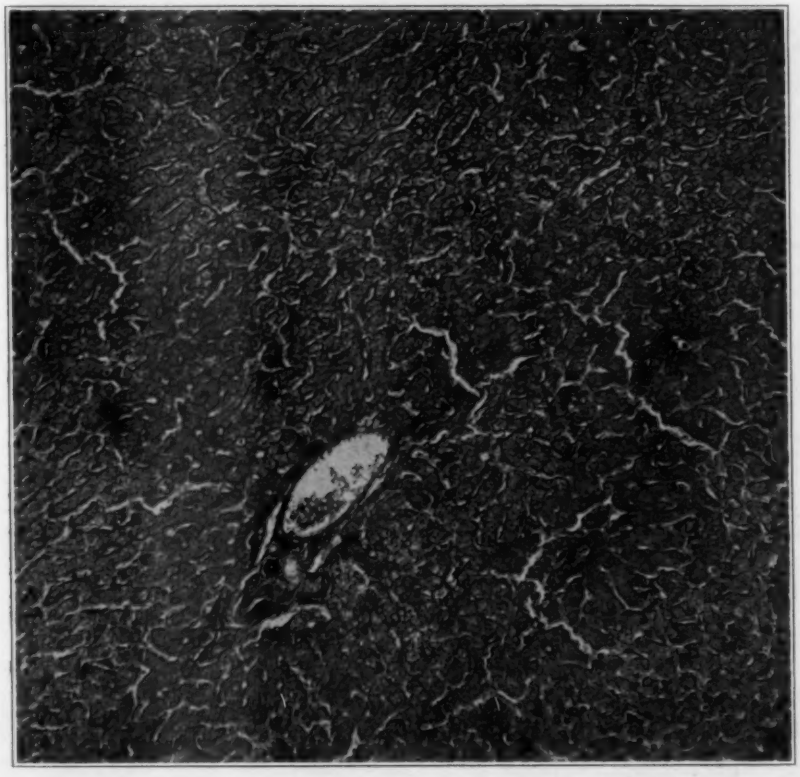

Fig. 10.—Low power photomicrograph of a section of the normal liver of a dog. Compare with figures 2 and 6.

to the stomach in experimental animals in itself does not entail marked hepatic infection. The conditions of the present experiment were planned to minimize the exposure of the gallbladder to contamination, and the pathologic results suggest that this has been accomplished no matter what the bacteriologic results are. These observations taken in conjunction with the paucity of recorded specific evidence of hepatic infection following cholecystogastrostomy in man suggest strongly that the fear of this sequel is unjustified. The results of the present

series of experiments removes the only plausible experimental evidence supporting the sequence of hepatic infection following cholecystogastrostomy.

In view of the fact that these conclusions are somewhat opposed to general surgical thought and to previous experimental work, it seems wise to reserve a final opinion as to their validity until this work has been repeated in other laboratories and with larger numbers of animals. The work of Weinberg [15] and his collaborators on cholecystogastrostomy in a monkey may be mentioned again here.

If these results are substantiated, it becomes obvious that there is no need to devise any other clinical operation for the purpose of short-circuiting the biliary system. The historical evidence seems to point to this operation in preference to cholecystenterostomy. As has been said, no reports of infection have been found following cholescystogastrostomy, whereas several have been found following cholecystenterostomy. Let me repeat that it is not wise to assume from these statements that no such instances have occurred. The only objection to cholecystogastrostomy so far advanced is removed.

It is to be noted that the six perforations of jejunal ulcers in this series occurred after the second stage. The exposure of the jejunum to unmodified gastric contents originated at the time of the Polya-Balfour anastomosis (first stage). It is hard to imagine how the delivery of bile into the duodenum through the pylorus following cholecystogastrostomy can be physiologically different from the delivery of bile through the ampulla of Vater previous to that operation, so far as the chemical protection of the jejunal mucosa is concerned. In other words, it is unlikely that the cholecystogastrostomy itself has anything to do with the occurrence of the ulcers, in spite of this time relationship.

The quantitative relationships of the bacteria found in the closed stump of the stomach have been mentioned, and the relationship of these findings to the general experimental problem has been discussed. A word or two may be said about the qualitative bacterial findings. From a study of cultures taken from the liver and bile there was found no relationship between the type of organism and the degree or character of the hepatitis. No organisms were recovered from three livers that showed definite hepatitis, and organisms were on several occasions recovered from a liver that showed no hepatitis.

CONCLUSIONS

A study of the literature of cholecystogastrostomy has shown a fear of hepatic infection as a sequel to the operation, without confirmatory evidence in the form of clinical, operative or postmortem reports of cases.

The results of previous experimental attacks on the problem confirm this fear. These, however, are subject to serious criticism in their application to the human being.

By creating a gastric pouch separated from the current of food, cholecystogastrostomy can be performed on the dog under conditions more nearly comparable bacteriologically with those under which the operation is performed in the human being.

In twenty-five dogs the performance of the preliminary operation on the stomach resulted in hepatitis. This pathologic change is less in degree than that resulting from the ordinary experimental performance of cholecystogastrostomy.

In twenty-two dogs on which cholecystogastrostomy was performed in a gastric pouch closed at the upper end the hepatitis found at various periods after the second stage operation was no greater in degree than that found following the preliminary operation.

The evidence presented, therefore, tends to discredit the common opinion among surgeons that hepatic infection is a dangerous sequel to cholecystogastrostomy.

EXPERIMENTAL STUDIES ON PULMONARY SUPPURATION

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In 1819 Laennec [1] published the first authentic report of a case of pulmonary gangrene. Subsequently, cases were noted by Leyden and Jaffe [2] (1866), who first noted the presence of spirochetes and other bacteria in the sputum and gangrenous tissue of patients suffering from this disease. The work of Rona [3] (1905) and especially that of Castellani [4] in 1906 attracted the attention of the medical profession to the possible etiologic relationship of the spirochetes to bronchopulmonary lesions. For the next decade heated controversies were waged, especially in France, with regard to the rôle played by the various anaerobes in pulmonary suppuration. A voluminous literature was evolved, filled with hypotheses but surprisingly lacking in experimental and clinical data.

CONCEPTS OF ETIOLOGY IN THE LITERATURE

In 1919 Heuer and Holman [5] made the first attempt to produce a pulmonary abscess by placing infected bullets in pulmonary tissue. Following numerous attempts one small abscess was produced. Aschner [6] in 1922 referred to numerous unsuccessful attempts to produce an abscess of the lung by the introduction of infected material into the bronchial tree. Fetterolf and Fox [7] in 1923 were the first

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2. Leyden, E., and Jaffe, M.: Ueber putrid Sputa, nebst einigen Bemerkungen über Lungenbrand und putrid bronchitis, Deutsches Arch. f. klin. Med. **2**:488, 1867.

3. Rona, S.: Zur Aetiologie und Pathogenese der Angina, der Stomatitis gangraenosa, des Noma und der Lungengangrän, Arch. f. Dermat. u. Syph. **74**: 171, 1905.

4. Castellani, A.: Note on a Peculiar Form of Hemoptysis with the Presence of Numerous Spirochaetae in the Expectoration, Lancet **1**:1384, 1906.

5. Heuer, G., and Holman, E., cited by Holman: Experimental Studies in Pulmonary Suppuration, Surg., Gynec. & Obst. **44**:328, 1927.

6. Aschner, P. W.: The Pathology of Lung Suppuration, Ann. Surg. **75**: 321, 1922.

7. Fetterolf, G., and Fox, H.: The Reaction of Peritonsillar Tissues to Tonsillectomy, Am. J. M. Sc. **166**:802, 1923.

to suggest the possible etiologic relationship of septic emboli when they succeeded in producing definite pulmonary abscesses by the injection of bits of tonsillar tissue into the jugular vein. In the same year Kline and Blankenhorn [8] produced pleuropulmonary gangrene in one rabbit by the intrabronchial injection of material from a carious tooth. Lambert and Miller [9] in 1924 injected a mixed culture of pure anaerobes intravenously into rabbits and after many failures produced one abscess of the lung, which occurred subsequent to the development of suppurative thrombophlebitis at the point of the injection. In 1925 Ribierre and Kermorgant [10] reported the production of hemorragic bronchitis by the intrabronchial injection of a culture of spirochetes. In 1926 Cutler and Schleuter [11] produced acute pulmonary abscess regularly by the introduction of emboli containing varous aerobic organisms. Their later studies [12] showed that the virulence of the organisms and the resistance of the host were of great importance. Holman, Chandler and Cooley [13] demonstrated that tuberculous emboli introduced into the jugular vein initiated the pathologic changes in the pulmonary tissue resulting successively in anemia, infarction, caseation, central softening and the formation of an abscess. In 1927 C. E. Smith and Rusk [14] and D. T. Smith [15] reported the production of all types of acute and chronic fusospirochetal disease in the lungs of mice, guinea-pigs and rabbits by the intratracheal injection of sputum and scrapings from the crypts of pyorrhea alveolaris. About the same time Ghiron and Maddalena [16] produced abscess by the introduction of a segment of vein containing gastric and intestinal contents into the jugular vein. Crowe and Scarff [17]

8. Kline, B. S., and Blankenhorn, M. A.: Spirochaetal Pulmonary Gangrene, J. A. M. A. **81**:719 (Sept. 1) 1923.

9. Lambert, A. V. S., and Miller, J. A.: Abscess of the Lung, Arch. Surg. **8**:446 (Jan.) 1924.

10. Ribierre, P., and Kermorgant, Y.: Pulmonary Spirochaetosis, Compt. rend. Soc. de biol. **93**:1351, 1925.

11. Cutler, E. C., and Schleuter, S. A.: The Experimental Production of Abscess of the Lung, Ann. Surg. **84**:256, 1926.

12. Cutler, E. C.; Halloway, J. W., and Schleuter, S. A.: Reaction of Immunity Through Experimental Production of Abscess of the Lung, Ann. Surg. **86**: 165, 1927.

13. Holman, E.; Chandler, L. R., and Cooley, C. L.: Experimental Studies in Pulmonary Suppuration, Surg., Gynec. & Obst. **44**:328, 1927.

14. Smith, C. E., and Rusk, G. T.: Pulmonary Spirochaetosis, Am. J. Path. **3**:225, 1927.

15. Smith, D. T.: Experimental Aspiratory Abscess, Arch. Surg. **14**:231 (Jan.) 1927.

16. Ghiron, V., and Maddalena, P.: Sulla produzione sperimentale di polmonite e gangrene pulmonari, Bull. atti. d. v. Accad. med. di Roma **53**:302, 1927.

17. Crowe, S. J., and Scarff, J. E.: Experimental Abscess of the Lung in the Dog, Arch. Surg. **16**:176 (Jan.) 1928.

in 1928 reported the production of abscess of the lung in eight dogs by the implantation in the bronchus of a pledget of cotton soaked in pyorrheal scrapings. They also reported the occurrence of abscess subsequent to the production of a foul sinusitis caused by the introduction of pyorrheal scrapings into the frontal sinus. In the same year Allen [18] reported the production of multiple abscesses in 100 per cent of his animals following the intrabronchial inoculation of warm sputum, provided the bronchus was ligated immediately following the injection. In 1928 Herrmann, Cutler and Weidlein [19] modified the original Cutler-Schleuter method and produced chronic abscess of the lung by an embolus impregnated with pyorrheal exudate. David T. Smith at this time reported being unable to produce suppuration of the lung by the intrabronchial injection of pure cultures of the anaerobes into guinea-pigs. In 1929 Lambert and Weeks [20] noted that when washed sputum containing both aerobes and anaerobes was used the abscess produced contained only anaerobes, the aerobes having disappeared.

The bacteriologic study of numerous clinical abscesses of the lung has revealed a bacterial flora similar to that of an unhygienic buccal cavity. The strongest argument for the theory of aspiration is the close similarity of the organisms of pulmonary suppuration to those found in the upper respiratory tract. Daily and Daily [21] reported the aspiration of blood in 78 per cent of one hundred patients during tonsillectomy while under general anesthesia. Iglauer [22] found blood in the trachea in 30 per cent of his cases (fifty) after local anesthesia. Myerson [23] showed bacterial contamination in 76 per cent of a large series of patients who underwent tonsillectomy, even though the head was tilted back at an angle of 45 degrees. He drew the pertinent conclusion that bland substances, such as mucus, saliva and blood, do not stimulate the mucosa of the larynx and trachea sufficiently to excite cough. Only when the mass of aspirated material is sufficient to interfere with the passage of air or when the mucosa is hyperirritable and inflamed is the cough reflex called into play. This fact of frequent

18. Allen, D. S.: Etiology of Abscess of Lung, Arch. Surg. **16**:179 (Jan.) 1928

19. Herrmann, L. G., and Cutler, E. C.: A Method for the Experimental Production of Chronic Abscess of the Lung, Proc. Soc. Exper. Biol. & Med. **26**:28 (Oct.) 1928. Weidlein, I. P., and Herrmann, L. G.: Abscess of the Lung: Experimental Studies in Chronicity, J. A. M. A. **91**:850 (Sept. 22) 1928.

20. Lambert, A. V. S., and Weeks, C.: Experimental Production of Abscess of Lung, Arch. Surg. **18**:446 (Jan.) 1929.

21. Daily, L., and Daily, R. K.: Bronchoscopic and Esophagoscopic Operations in Tonsillectomies, Texas State J. Med. **23**:277 (Aug.) 1927.

22. Iglauer, S.: Post-Tonsillectomy Lung Abscess, Ann. Otol., Rhin. & Laryng. **37**:231, 1928.

23. Myerson, M. C.: Pulmonary Aspects of Tonsillectomy Under General Anesthesia, Laryngoscope **32**:929, 1922.

contamination of the lower portion of the respiratory tract is the strongest argument against the hypothesis of aspiration as the origin of abscess of the lung. Myerson reported an evacuation time of twelve minutes in the lower portion of the respiratory tract owing to ciliary action and bronchial peristalsis. Hedblom and his associates [24] suggested that in certain instances the mechanism of elimination fails and that fluid may gravitate out into the periphery beyond the field of the scavenging activity of cough and ciliary action. Archibald [25] found that when substances were aspirated beyond a certain zone in the bronchial tree cough had the effect of driving them farther toward the periphery.

In short, both clinical and laboratory experience has demonstrated the lung to be very susceptible to the formation of abscess from septic embolism and to be very resistant to bronchogenic inoculation. Certain types of abscess are purely embolic; others are purely bronchogenic, but a large group is not explained by either mode of origin. For these cases certain investigators (Holman and Mathes; [26] Van Allen, Adams and Hrdina [27]) suggested the combination of the embolic route and aspiration. Holman and Mathes reported hemorrhagic infarction in twenty-eight of thirty-two animals following the introduction of one sterile and one infected embolus. Van Allen and his associates, on the other hand, suggested that septic embolism produces the initial acute abscess which is secondarily invaded by intrabronchial contaminating organisms, which in turn exert a profound effect on the chronicity and the virulence of the preexisting abscess of the lung. This accounts in the embolic theory for the disparity between the existing bacterial flora of the abscess and that of the operative field. It also shows why the organisms normally resident in the upper portion of the respiratory tract are found in abscesses of the lung despite the difficulty of producing experimental bronchiogenic lesions.

EXPERIMENTAL STUDIES

To recapitulate: Pulmonary abscess may be pictured bacteriologically as originating from an uncertain agent but ending in a definite

24. Hedblom, C. A.: Pulmonary Abscess and Bronchiectasis, Etiology and Diagnosis, Long Island M. J. **92**:378, 1930. Hedblom, C. A.; Joannides, M., and Rosenthal, S.: Pulmonary Suppuration, Ann. Surg. **88**:823, 1928.

25. Archibald, E. W., and Brown, A. L.: Dangers of Introducing Iodized Oil into the Tracheo-Bronchial Tree, J. A. M. A. **88**:1310 (April 23) 1927.

26. Holman, E., and Mathes, M. E.: The Production of Intra-Pulmonary Suppuration by the Secondary Infection of a Sterile Embolic Area, Arch. Surg. **19**: 1246 (Dec.) 1929.

27. Van Allen, C. M.; Adams, W. E., and Hrdina, L. A.: Embolism in Bronchiogenic Infection of the Lung, Arch. Surg. **19**:1279 (Dec.) 1929.

clinical picture that includes a terrific secondary invasion of organisms of various and diverse types. Several questions immediately present themselves:

1. What organisms or group of organisms is responsible for the original infection?

2. Does the study of bacterial invasion reveal anything with regard to the pathogenesis of pulmonary suppuration?

3. In what ways do the course and prognosis of these lesions depend on the organisms or group of organisms present?

The theories with regard to a specific initial infection rest on very uncertain data. The most logical assumption is that a number of

TABLE 1.—*Results of Experiments with Intrabronchial Implantation*

Experiment	Dog	Material Implanted*	Cause of Death	Duration of Roentgenographic Signs	Lesion Found at Autopsy
1	4	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
2	5	S. E., B. coli (virulent); Br.	Pneumonitis	Two days	Pneumonitis and empyema
3	7	S. E., B. coli (virulent); Br.	Killed	No lesion	No pulmonary lesion
4	6	S. E., pyorrhea; Br.	Killed	No lesion	Fibrosis about lead shot
5	312	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
6	313	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
7	314	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
8	26	S. E., pyorrhea; Br.	Distemper	No lesion	No pulmonary lesion
9	37	S. E., pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
10	10	Pyorrhea; Br.	Killed	No lesion	No pulmonary lesion
11	316	Pyorrhea; Br.	Killed	No lesion	Early bronchiectasis
12	317	Pyorrhea; Br.	Killed	No lesion	No lesion
13	315	Pyorrhea; Br.	Killed	No lesion	Early bronchiectasis
14	11	Pyorrhea; implantation in frontal sinus	Killed	No lesion	No pulmonary lesion
15	57	Washings from antrum; Br.	Killed	No lesion	No pulmonary lesion
16	59	Washings from antrum; implantation into frontal sinus	Killed	No lesion	No pulmonary lesion
17	60	Washings from antrum; Br.	Killed	No lesion	No pulmonary lesion
18	56	Washings from antrum; Br.	Killed	No lesion	No pulmonary lesion

* S. E. means sterile embolus; Br., bronchoscopic implantation.

organisms are involved, but not the same ones in each case. As a clinical abscess represents an advanced stage, with considerable secondary flora present, it is within the range of probability that the original infectious agent has relatively little, if any, clinical significance.

Cognizant of the scope of this problem, we laid out a detailed, controlled group of experiments. This paper represents the preliminary report. In the first place, a series of experiments was planned in order to contrast the mode of bacterial invasion with relation to the pathogenesis of the lesion.

The endobronchial approach was tried in eighteen dogs. Previous to bronchoscopic implantation of infectious material the cough reflex was abolished by the administration of ½ grain (0.03 Gm.) of morphine and the bronchial mucosa was cocainized. Following the bronchoscopy performed with the dog under ether anesthesia, the animal was given

TABLE 2.—*Results of Experiments with Embolic Implantation of a Vein Segment in the Jugular Vein*

Experiment	Dog	Material	Duration of Lesion, Days	Cause of Death	Lesion at Autopsy
1	13	Pyorrhea	15	Pulmonary hemorrhage	Abscess of lungs
2	14	Pyorrhea	120	Convulsions; killed	Abscess of lung; cerebral embolism
3	15	Pyorrhea	20	Killed in fight	Abscess of lung
4	16	Pyorrhea	150	Cerebral embolism; convulsions	Abscess of lung
5	22	Pyorrhea	80	Killed	Abscess of lung (chronic)
6	33	Pyorrhea	6	Empyema	Empyema; abscess of lung
7	63	From abscess in dog 24	35	Killed in fight	Abscess of lung (chronic)
8	67	From abscess in dog 22	86	Killed	Abscess of lung (chronic)
9	105	From abscess in dog 39	90	Killed	Abscess of lung (small)
10	106	From abscess in dog 39	185	Killed	No demonstrable lesion
11	8	Pyorrhea	230	Killed	Epithelized cavity (no activity)
12	12	Pyorrhea	155	Killed	Area of fibrosis (no activity)
13	193	Pyorrhea	36*	Killed	Abscess of lung
14	194	Pyorrhea	40*	Killed	Abscess of lung
15	208	Pyorrhea	26*	Killed	Abscess of lung
16	278	Pyorrhea	13	Toxemia	Abscess of lung
17	308	Pyorrhea	26*	Empyema	Abscess of lung
18	311	Pyorrhea	41*	Killed	Abscess of lung
19	286	From abscess in dog 193	30	Killed	Large abscess of lung

* The involved lung was removed by pneumonectomy.

TABLE 3.—*Results of Experiments with Embolic Implantation of Blood Clot in the Jugular Vein*

Experiment	Dog	Material	Duration of Lesion, Days	Cause of Death	Lesion at Autopsy
1	17	Pyorrhea	20	Empyema	Abscess of lung; empyema
2	18	Pyorrhea	42	Empyema	Abscess of lung; empyema
3	19	Pyorrhea	65	Killed	No demonstrable lesion
4	20	Pyorrhea	58	Killed	Abscess of lung
5	23	Pyorrhea	4	Empyema; convulsions	Abscess of lung; empyema
6	24	Pyorrhea	47	Killed	Chronic abscess of lung
7	32	Pyorrhea	9	Empyema; pulmonary hemorrhage	Abscess of lung; empyema
8	35	Pyorrhea	23	Pulmonary hemorrhage	Abscess of lung
9	39	Pyorrhea	110	Killed	Chronic abscess of lung
10	40	Pyorrhea	158	Killed	Chronic abscess of lung
11	43	Pyorrhea	75	Empyema	Abscess of lung; empyema
12	44	Pyorrhea	34	Empyema	Abscess of lung; empyema
13	45	Pyorrhea	16	Empyema	Abscess of lung; empyema
14	47	From abscess in dog 24	7	Pulmonary hemorrhage	Abscess of lung; empyema
15	62	From abscess in dog 24	6	Pulmonary hemorrhage	Abscess of lung; empyema
16	49	From abscess in dog 24	45	Killed in fight	Abscess of lung; empyema
17	64	From abscess in dog 24	2	Distemper	Hemorrhagic pneumonitis
18	81	From abscess in dog 22	16	Killed in fight	Abscess of lung
19	84	From abscess in dog 22	8	Killed in fight	Abscess of lung
20	85	From abscess in dog 22	26	Found dead in cage	Abscess of lung
21	88	From abscess in dog 22	30	Distemper	Abscess of lung; distemper

¼ grain (0.015 Gm.) of morphine. Cotton plugs impregnated with infectious material (such as scrapings from the gingival trenches of patients with pyorrhea alveolaris and washings from the antrum) were implanted in the secondary and tertiary bronchi of seven dogs by means of the bronchoscope. In nine animals the resistance of a certain portion of the pulmonary parenchyma was lowered previous to intrabronchial implantation by the release of sterile emboli in the form of segments of veins into the jugular vein. In two other dogs the material was implanted in the frontal sinus. The animals were closely observed, but in no case did a pulmonary abscess develop (table 1). In two of the animals signs of early bronchial ulceration and dilatation (early

Fig. 1.—A chronic abscess of the lung produced by the embolic implantation of scrapings from crypts of pyorrhea alveolaris in vein segments, showing the zone of infiltration about the abscess and illustrating the rupture of the abscess into the bronchus. The specimens were obtained by pneumonectomy.

bronchiectasis) were noted at autopsy, beyond the point of occlusion of the bronchus by the cotton plug (fig. 2). The distal bronchus was filled with a mucopurulent secretion, but in no case was any area of localized pulmonary necrosis found, despite the fact that many of the animals were killed from forty-two to seventy days after the bronchoscopic implantation.

In another series of forty dogs the infectious material was introduced in the form of emboli (vein segment or blood clot), Herrmann's modification of the original Cutler-Schleuter technic being used. In most instances the infectious material was scrapings from the gingival trenches

of patients with protracted pyorrhea alveolaris. In some cases the material was derived from an abscess of the lung of a killed animal. This series was divided into two groups: (1) that in which the vein segments were used as emboli (table 2), and (2) the group in which blood clots were used (table 3). A parallel analysis of both groups disclosed interesting data, to be taken up later. In this series 92.5 per cent of the animals were found to have an abscess of the lung at

Fig. 2.—Ulceration of the bronchial mucosa such as was noted distal to the point of bronchial occlusion in several cases of endobronchial implantation. The specimen was obtained by pneumonectomy.

autopsy. One animal died of hemorrhagic pneumonitis. In only two animals were no lesions demonstrable at autopsy, and they were killed sixty-five and one hundred and eighty-five days, respectively, after the introduction of emboli. The abscesses formed varied from acute abscesses found in the animals dying in from four to nine days of empyema or pulmonary hemorrhage to chronic abscesses of from one

hundred and ten to one hundred and fifty days in duration. In an animal killed at the end of two hundred and thirty days an epitheliated cavity was found with no surrounding activity, simulating the epitheliated cavity found occasionally in an old clinical case of abscess of the lung when the infection has burned itself out but has left a defect too great for nature to repair.

It is interesting to note that the incidence of fatal empyema was only 10 per cent in animals into which a vein segment was introduced, as

Fig. 3.—A pulmonary abscess which ruptured into the pleural cavity, producing empyema which was fatal.

against the incidence of 33 per cent in animals into which the organisms were introduced in clotted blood as emboli. It is also interesting to note that fatal pulmonary hemorrhage occurred in 5 per cent of the animals into which a vein segment was introduced as against an incidence of 19 per cent in those into which a blood clot was introduced. These facts point out the ability of pulmonary tissue to acquire greater local resistance when not subjected to a sudden overwhelming bacterial invasion simultaneously with the damage produced by the infarction.

Tuttle and Nicoll [28] showed the effect of ligation of the pulmonary artery on the healing time of experimental abscess of the lung. Holman, Mathes and Reichert [29] demonstrated clearly that the occlusion of a branch of the pulmonary artery to a pulmonary lobe leads invariably to marked dilatation of the bronchial artery to that lobe, so that the pulmonary artery in the embolic area is eventually fully supplied

Fig. 4.—A large cavity of a pulmonary abscess produced by an embolus containing the mixed flora of pyorrhea alevolaris which had been stepped up in virulence by animal-to-animal passage. The animal died of toxemia.

with blood. This is brought about usually by the dilatation of the bronchial artery and occasionally by the establishment of capillary

28. Tuttle, W. M., and Nicoll, G. L.: Effect of Pulmonary Artery Ligation on the Healing Time of Experimental Pyogenic Lung Abscesses in Dogs, J. Thoracic Surg. **2**:60 (Oct.) 1932.

29. Holman, E.; Mathes, M. E., and Reichert, F. L.: A Study of the Bronchial, Pulmonary and Lymphatic Circulations of the Lung Under Various Pathologic Conditions Experimentally Produced, J. Thoracic Surg. **1**:339 (April) 1932.

anastomosis with the branch of the pulmonary artery adjoining the infarcted area. Those workers also showed that the bronchial artery is invariably dilated to a marked degree in the presence of an infected embolus. This is undoubtedly an important factor in accounting for the difference in the course of the suppurative lesions in the two groups. It is interesting to note the close clinical parallelism in the fact that

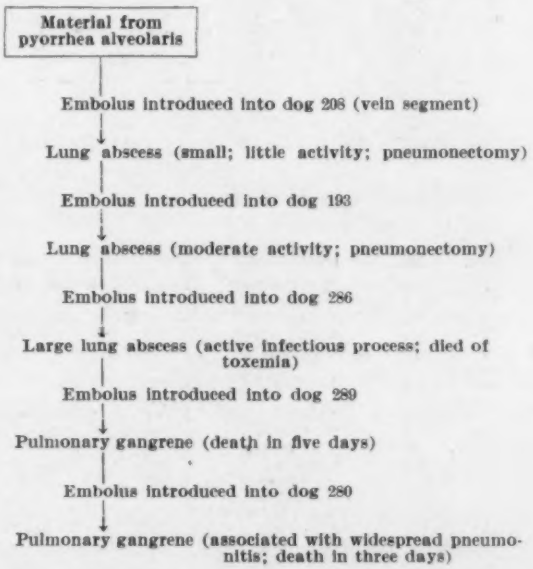
Fig. 5.—Pulmonary gangrene produced by an embolus containing the mixed flora of pyorrhea alveolaris which had been stepped up to the highest virulence. Note the diffuse cavitation and the definite line of demarcation.

in two of the animals there developed signs of cerebral embolism one hundred and twenty and one hundred and fifty days after the implantation of the emboli.

A series of experiments was then planned to determine the relation of the virulence of the mixed bacterial flora to the clinical course of

pulmonary suppuration. Table 4 indicates clearly the gradual stepping up in virulence produced by animal-to-animal passage of infectious material derived from a patient with chronic pyorrhea alveolaris. At first only a small abscess of the lung was produced, with little activity. The lung was removed by pneumonectomy, and a small portion of the contents of the abscess were transplanted in a vein segment as an embolus into dog 193, in which there developed a somewhat larger abscess which displayed moderate activity. The material from this animal was passed on to dog 286, in which there developed a large

TABLE 4.—*Results of Experiments Showing Stepping Up of the Virulence of Mixed Bacterial Flora*


Material from pyorrhea alveolaris
Embolus introduced into dog 208 (vein segment)
Lung abscess (small; little activity; pneumonectomy)
Embolus introduced into dog 193
Lung abscess (moderate activity; pneumonectomy)
Embolus introduced into dog 286
Large lung abscess (active infectious process; died of toxemia)
Embolus introduced into dog 289
Pulmonary gangrene (death in five days)
Embolus introduced into dog 280
Pulmonary gangrene (associated with widespread pneumonitis; death in three days)

abscess of the lung; the dog died of toxemia. In the next animal typical pulmonary gangrene developed, and death occurred in five days. Autopsy revealed pulmonary gangrene which was lobar in distribution and accompanied by widespread cavitation (fig. 5). The last animal of the series died in three days of pulmonary gangrene associated with widespread pneumonitis. In short, we noted the entire transition in virulence of the mixed flora from that producing a small area of localized necrosis (pulmonary abscess) to that producing diffuse pulmonary gangrene. Since the flora remained the same, the differences were due to a stepping up of the virulence of the separate organisms.

Having compared the relation of the various modes of bacterial invasion and having studied the relation of the virulence of the mixed

bacterial flora to the pathogenesis and type of pulmonary pathologic process produced, we isolated the various organisms from the mixed bacterial flora and grew them in pure culture. Elaborate aerobic and

TABLE 5.—*Results of Experiments with Embolic Implantation of Organisms in Pure Culture (Series 1)*

Experiment	Dog	Organisms	Embolus Located by Roentgen Examination	Findings in Resected Lung	Time Since Implantation, Days
1	229	Culture A	Yes	No lesion demonstrable	48
2	200	Culture B	Yes	No lesion demonstrable	50
3	320	Culture C	Yes	No lesion demonstrable	52
4	321	Culture D	Yes	No lesion demonstrable	52
5	304	Culture E	Yes	No lesion demonstrable	53
6	322	Culture F	Yes	No lesion demonstrable	54
7	323	Culture G	Yes	No lesion demonstrable	56
8	324	Culture H	Yes	No lesion demonstrable	57
9	325	Culture I	Yes	No lesion demonstrable	59
10	326	Culture J	Yes	No lesion demonstrable	59
11	279	Culture K	Yes	No lesion demonstrable	60
12	319	Culture L	Yes	No lesion demonstrable	62

TABLE 6.—*Results of Experiments with Embolic Implantation of Organisms in Pure Culture (Series 2)*

Experiment	Dog	Organisms	Cause of Death	Lesion Found at Autopsy	Time Since Implantation, Days
1	30	B. coli virulent)	Killed	Area of fibrosis in lung	47
2	50	Culture A	Killed	Small area of fibrosis in lung	83
3	52	Culture B	Killed	Small area of fibrosis in lung	83
4	51	Culture D	Pneumonitis	Diffuse pneumonitis (right lung)	3
5	54	Culture E	Killed in fight	Area of fibrosis (no activity)	44
6	46	Culture F	Killed	No lesion	122
7	71	Culture G	Killed	Area of fibrosis (no activity)	70
8	80	Culture H	Killed	No lesion	79
9	104	Culture J (anaerobic hemolytic streptococcus)	Killed	Small area of fibrosis	190
10	107	Culture K (Spirochaeta microdentium in agar cubes)	Killed	No lesion demonstrable	151
11	108	Culture L (Spirochaeta macrodentium in vein segment)	Killed	No lesion demonstrable	150
12	109	Culture M (anaerobic; in abscess of lung of patient)	Killed	No lesion demonstrable	147
13	102	Culture N (Bacterium melaninogenicum; anaerobic hemolytic streptococcus)	Killed	No lesion demonstrable	180

anaerobic cultures (prepared by a method described by Herrmann [30]) were made on special mediums, with the pabulum require-

30. Herrmann, Louis G.: An Improved Method for the Cultivation of Anaerobic Microörganisms, J. Bact. **23**:331 (April) 1932.

ments and hydrogen ion concentration to meet the specific demand of each organism. Two separate strains of aerobes and anaerobes (used in producing abscess of the lung) were plated out. The organisms grown in pure culture were introduced individually in vein segments into two new series of animals. The emboli were located by roentgenograms and their position was rechecked by weekly roentgen examination. In one series the animals were killed. In the other series, in which the animals were spared, the lung in which the embolus had lodged, as checked by roentgen examination, was removed by pneumonectomy from forty-eight to sixty-two days after implantation. In no animal of either series could an abscess be noted (tables 5 and 6).

Our next step will be to determine which combination of these organisms has a proteolytic action on tissue in vitro. The effect of these combinations will then be studied in vivo. Later emboli containing the various proteolytic combinations will be introduced into the jugular vein of dogs, and the action of respective combinations on pulmonary tissues will be studied in an attempt to find out which group of organisms produces clinical abscess of the lung. It is hoped that time permits us to combine the embolic and intrabronchial lines of attack in the attempt to determine, if possible, the organisms or group of organisms which act as the vanguard, preparing the way for the advance of the necrotizing proteolytic bacterium or group of bacteria. Through this maze of experimental work, we have the patient as our guide. To this end we hope to make clinical application of the phenomena of desensitization as studied and applied by Dorst and Wherry.[31]

SUMMARY AND CONCLUSIONS

The various concepts of the etiology of pulmonary suppuration have been reviewed. The bacteriologic studies of numerous clinical abscesses of the lung reveal bacterial flora similar to that of an unhygienic buccal cavity. This similarity of organisms suggests aspiration as the possible cause. However, the relative infrequency of pulmonary abscess as against the frequency of bronchial contamination following operations on the upper respiratory passages may be taken as the strongest argument against the hypothesis of aspiration as the source of infection.

Experimentally it has been demonstrated that the lungs are susceptible to the formation of abscesses from septic embolism but are

31. Dorst, S., and Wherry, W. B.: Local Skin Reactions in the Selection of Antigens for Autogenous Vaccines, Ohio State M. J. **24**:539 (July) 1928. Wherry, W. B.: Hypersensitivity to Bacterial Proteins and Its Rôle in Susceptibility and Immunology, Am. J. Hyg. **14**:539, 1931.

very resistant to bronchogenic inoculation. Certain abscesses are purely embolic and others are purely bronchogenic, but a great number are not explained by either mode of origin. For these a combination of both mechanisms may eventually account for the disparity between the existing bacterial flora of the abscess and that of the operating field. Pulmonary abscess may be pictured bacteriologically as originating from an uncertain agent but ending in a definite clinical picture that includes a terrific secondary invasion of organisms of various and diverse types. The theories with regard to specific initial infection rest on very uncertain data.

Cognizant of the scope of this problem, we laid out a detailed and well controlled group of experiments. To contrast the modes of bacterial invasion in relation to the pathogenesis of the lesion, the endobronchial and the embolic approach were tried. In sixteen animals the material (scrapings from the gingival trenches of persons with pyorrhea alveolaris) was introduced into the secondary and tertiary bronchi by means of a bronchoscope. In spite of the fact that the cough reflex was abolished and the bronchus occluded with the plug, in no case did a pulmonary abscess develop. In two of the animals signs of early bronchial ulceration and dilatation were noted beyond the point of occlusion of the bronchus by the cotton plug. In two other animals the material was introduced into the frontal sinus. No abscess was produced. In a series of forty animals, the infectious material was introduced in the form of emboli (vein segment or blood clot). In this series 92.5 per cent of the animals were found to have an abscess of the lung at autopsy. The abscesses produced varied from acute abscesses found in animals dying of empyema or of pulmonary hemorrhage to chronic abscess of from one hundred and ten to two hundred and thirty days' duration. The incidence of death caused by empyema in the group receiving the vein segments was 10 per cent, as against 33 per cent in the group receiving the blood clots. The incidence of fatal pulmonary hemorrhage was 5 per cent in the former group as against 19 per cent in the latter. These facts point out the ability of pulmonary tissues to develop (through secondary dilatation of the bronchial arteries, etc.) an excellent local protective mechanism when not subjected to a sudden overwhelming bacterial invasion simultaneously with the damage produced by the infarction.

In another series of experiments planned to determine the relation of the virulence of the mixed bacterial flora to the clinical course of pulmonary suppuration, the complete transition in virulence was noted from that producing a small area of localized necrosis (pulmonary abscess) to that producing diffuse pulmonary gangrene. The stepping up in virulence was accomplished by animal-to-animal passage of the organisms.

Two distinct mixed bacterial strains used in producing pulmonary abscesses were plated out, and the separated aerobes and anaerobes grown in pure culture were introduced individually in vein segments into two series of animals. But in no animal of either series did a chronic abscess of the lung develop. At present studies are being made of the action of various combinations both in vitro and in vivo in an attempt to determine, if possible, the exact nature of their synergistic bacterial action.

MESENTERIC LYMPHADENITIS SIMULATING ACUTE APPENDICITIS

QUANTITATIVE STUDY OF THE SIZE OF NORMAL MESENTERIC LYMPH NODES

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Enlargement of the lymph nodes of the mesentery has been recognized since the eighteenth century. Bertein and Worms credited Sydenham with the earliest description of mesenteric tumors or enlargements in children. The term "strumous abdomen" was used during the early nineteenth century to describe the condition. "Tabes mesenterica," a term which has endured, was first introduced in 1775 by Ball.

The diagnosis of the disease during life was usually a conjecture, and it was recorded as a fact only when the disease was seen at autopsy. All necropsy observations during this early period indicated that the process was tuberculous. The condition was not commonly recognized at the beginning of the twentieth century, and was regarded as a pathologic curiosity as recently as 1905 (Branson). Mächtle, in 1909, published the first summary from the surgical literature, and only fourteen cases were recorded. The paucity of cases undoubtedly accounts for the relatively little attention which the disease process attracted.

During the early years of the twentieth century, however, the condition began to provoke surgical attention. This was probably because of the increased frequency with which surgical exploration of the abdomen was performed for the relief of acute disease processes. Enlargement of the mesenteric lymph nodes was frequently encountered as the only etiologic factor in the production of acute abdominal symptoms. Cases were described by Richardson wherein the symptoms were those of acute appendicitis, but which revealed on surgical exploration merely an enlargement of the mesenteric lymph nodes and no appendical pathologic condition. Some of the enlarged nodes showed caseation, suppuration or calcification, while others appeared to be only mildly inflamed. All the nodes were thought to present a tuberculous process (Branson; Corner, 1905 and 1908; Shiota; Fordyce; Thiemann; Newbolt; Floderus; Lund; Still; Carson; Iselin). Consequently, the condition soon received attention as a distinct surgical entity.

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A brief description of such a case encountered in the surgical service of the University of Minnesota Hospital will serve as an illustration of the disease process.

REPORT OF A CASE

History.—A white boy, 2.5 years of age, was admitted to the University of Minnesota Hospital on July 19, 1929, and discharged on July 27. The patient was well until two weeks before admission, when marked anorexia developed. Six days before entrance he complained of abdominal pain, and the mother thought that he had a fever. Four days later he complained of more severe pain, which he localized in the right lower quadrant of the abdomen. There had been neither nausea nor emesis. Defecations had been regular and the stools normal. A physician was consulted, who found the child to have a temperature of 102 F. and marked tenderness in the right lower quadrant of the abdomen. The child was immediately referred to the University Hospital with a diagnosis of acute appendicitis. The remaining history was normal as was the family history.

Physical Examination.—The child appeared to be well developed and well nourished. Respirations were somewhat labored. The temperature was 102 F., and the pulse rate was 120. There was neither localized nor generalized lymphadenopathy. Cardiac and pulmonary observations were normal. The abdomen was prominent, and was tense on palpation. Tenderness was noted in the right lower quadrant, but muscle spasm and rigidity were questionable. There were no palpable abdominal masses, and shock *en retour* was absent. A rectal examination revealed no abnormalities.

Laboratory Data.—The urine was normal except for a few white blood cells in the urinary sediment. Examination of the blood showed: hemoglobin content, 72 per cent; red cell count, 4,350,000, and white cell count, 13,000, with polymorphonuclear neutrophils 51 per cent and lymphocytes 49 per cent. A roentgen examination of the chest showed no pathologic process.

Diagnosis and Therapy.—A diagnosis of acute appendicitis was made, and an operation was immediately performed. Numerous large, hard lymph nodes were noted throughout the mesentery of the small intestine, on opening the anterior abdominal wall through a McBurney incision. One group of nodes in the mesentery of the ascending colon felt like a lobulated kidney. The nodes were about 1 cm. in diameter, and presented a congestion of the vessels and a puckering of the peritoneum about them. Most of the large, hard nodes were found along the intestinal border of the mesentery. The appendix was normal in gross appearance. Appendectomy was done, but no biopsy was taken of the enlarged nodes. The postoperative diagnosis was that of acute adenitis of the mesenteric lymph nodes, of unknown origin. Histologic examination of the appendix showed it to be normal.

Postoperative Course.—The child's immediate convalescence was uneventful, and he was discharged from the hospital on the eighth postoperative day. He was not seen again until 2.5 years later, when he entered the University of Minnesota outpatient dispensary complaining of recurrent attacks of abdominal distress associated with emesis and diarrhea. The attacks occurred at intervals of about two months. The child's mother stated that he seemed to become fatigued easily. Further investigation of the history showed that the child had ingested milk from tuberculous cows a short time before the onset of the original acute abdominal symptoms.

In view of this history and the previous operative findings a Mantoux test was applied, and the result was positive. An x-ray picture of the abdomen was taken, which showed calcified mesenteric lymph nodes (fig. 1). Consequently the final diagnosis was tuberculosis of the mesenteric lymph nodes.

TUBERCULOUS MESENTERIC LYMPHADENITIS

Frequency.—The frequency of occurrence of tuberculous mesenteric lymph nodes has not been studied extensively. The earliest chrono-

Fig. 1.—A roentgenogram showing the calcified mesenteric lymph nodes mentioned in the description of the case of tuberculous mesenteric lymphadenitis.

logical investigations of this disease entity were based on observations of the condition at autopsies on tuberculous subjects and not on clinical considerations. Its frequent occurrence stimulated several studies of the relationship of tuberculous mesenteric lymphadenitis to tuberculosis elsewhere in the body (Rilliet and Barthez; Woodhead; Colman; Carr; Branson; Fordyce; Still). The condition was found to exist in as high as 79 per cent of cases with other primary tuberculous foci. Studies of the relationship of gastro-intestinal tuberculosis to tuberculosis

in other regions were undertaken at about the same time (Eisenhart; Haman; Conrath). The investigations showed that gastrointestinal tuberculosis was present in as many as 68 per cent of persons with tuberculosis in other parts of the body. A comparison of these figures suggested a relationship between tuberculosis of the digestive tract and tuberculosis of the mesenteric lymph nodes.

The frequent presence of tuberculous mesenteric lymphadenitis at autopsies on persons with tuberculosis stimulated investigations of its occurrence in general autopsy observations. Reports of several series of cases show the incidence of tuberculous mesenteric lymphadenitis to vary from 1 to 3 per cent (Osler and McCrae). The prevalence of the condition varies with the region of the world from which the figures were derived, the higher figures coming from certain sections of Scotland.

Finally, the incidence of the condition in general abdominal surgical practice was studied. It would be expected to be higher than that in general autopsy observations, because most abdominal explorations are based on the presence of intra-abdominal pathologic conditions. One investigation of this phase of the problem has been recorded in the literature (Braithewaite). The study covered a period of twelve years, during which time the surgeons were admonished to look especially for the condition. One would expect the ultimate figure of frequency to be higher than that derived from mere casual recognition of the condition; nevertheless only 0.74 per cent of 58,731 exploratory laparotomies showed evidence of tuberculous mesenteric lymphadenitis.

From the foregoing analysis it may be concluded that the occurrence of tuberculous mesenteric lymphadenitis is infrequent in general clinical experience. It is true that no large series of clinical cases has been reported. A good share of the literature concerning the frequency of occurrence of this clinical condition consists of reports of cases. Mächtle published a summary of fourteen cases from the surgical literature in 1908. Floderus published data in 1912 concerning eighteen cases of enlargement of mesenteric lymph nodes which he obtained during the preceding decade. Riseley described thirty operative cases in 1915, and Carson, in 1919, reported fifty operative cases encountered during an eight year period. Mettenleiter reported twenty-nine operative cases obtained over a ten year span, Ljunggren described sixty cases of mesenteric lymphadenitis encountered during four years, and Bagg reported thirty cases seen over an eight year period. Thus, it may be concluded that the scant study given the condition is due to its relatively infrequent occurrence.

Age.—Infancy and childhood are the periods of life in which tuberculosis of the mesenteric lymph nodes is most frequently encountered (Colman; Carr; Branson; Corner, 1905; Floderus; Lund; Parker;

Carson; Walker; Braithewaite; Osler and McCrae; Bell; Marshall). The condition is sometimes seen in young adults (Newbolt; Floderus; Riseley) and occasionally in the middle-aged, but by far the greatest number of cases are seen in children from the time of birth to 15 years of age.

Symptomatology.—No precise clinical syndrome for tuberculosis of the mesenteric lymph nodes has been established. The varying symptoms have been well described by many writers, but they differ somewhat in children and adults (Corner, 1905 and 1912; Floderus; Franke; Carson; Clute; Krogsgaard; Braithewaite; Ljunggren; Mettenleiter; Bagg; Auchincloss).

The condition may be present in either an acute or a chronic form. The acute type is usually marked by a sudden onset and complaints of severe, crampy abdominal pain, followed by nausea and emesis. The pain commences in the epigastrium or is generalized over the abdomen and localizes in the right lower quadrant. It is paroxysmal and sufficiently severe to cause the patient to double up and cry out. The attacks commonly occur from two to five times a day, and vary in duration from five minutes to two hours. The pain usually ceases as suddenly as it began, and all symptoms subside in two or three days.

Patients presenting the more chronic form complain of vague, intermittent, transitory attacks of colicky pain in the right lower quadrant or other regions of the abdomen. Often the complaint is not of pain but merely of a sensation of drawing or dragging in the abdomen. There is frequently a history of repeated attacks of indefinite gastric distress associated with nausea and emesis. Constipation and diarrhea are not common symptoms in the chronic form, but may be present in the acute attack. The chronic form is more common in young children, and the condition ultimately becomes acute.

The symptoms in older children and young adults are usually the same as those just described, but the clinical picture in the more advanced age group may be complicated by symptoms of dysphagia (Wakely), peptic ulcer (Thiemann; Lund; Bier; Keppler and Erkes; Davidovitch; Ljunggren; Golden and Reeves), biliary colic (Most; Pribram), intestinal spasm (Schalij), constipation or diarrhea (Sternberg), renal colic or hematuria (Schmieden; Walker; Davidovitch; Golden and Reeves) or even sciatica (Ljunggren).

Physical Findings.—Physical examination reveals abdominal tenderness and spasm and rigidity of the muscles over the tender area. The pain is frequently localized just to the right of the umbilicus above McBurney's point (Gehrels; Brentano; Auchincloss). Occasionally a mass may be palpated in the right lower quadrant of the abdomen (Floderus; Riseley; Braithewaite; Bagg). Rebound tenderness is common. Lymph nodes elsewhere in the body usually are not enlarged.

Rectal examination reveals no abnormalities. The pulse rate varies from 100 to 120, and the temperature is elevated from 100 to 104 F. (Fordyce; Bell). The general impression is that of a pronounced systemic reaction without the marked clinical findings one expects.

Laboratory Data.—Examination of the urine generally shows it to be normal. The white blood cell count varies from 12,000 to 17,000, the differential count showing about 80 per cent polymorphonuclear neutrophils.

Diagnostic Aids.—Roentgen examination of the abdomen often discloses the presence of calcified mesenteric lymph nodes. This procedure was used as early as 1905 by Corner for the diagnosis of tuberculosis of the mesenteric lymph nodes. It had received little attention in the literature as a diagnostic procedure, however, until the recent work of Strömbeck. He expressed the belief that the presence of calcified mesenteric lymph nodes is strongly indicative of tuberculosis, as such calcifications arise early and almost exclusively after the onset of a tuberculous process. In infants and young children it is common to find the Pirquet reaction positive (Head). It is now generally recognized, however, that a Pirquet reaction fails to occur in a fairly large percentage of persons known to be tuberculous. The incidence of positive skin reactions with tuberculin should be considerably higher therefore, following the widespread use of the more sensitive Mantoux intradermal test.

Diagnosis.—The differential diagnosis in children includes, primarily, acute appendicitis and, secondarily, Meckel's diverticulitis, intussusception and pyelonephritis. In older children and young adults the condition closely simulates acute appendicitis, but must also be differentiated from cholecystitis and cholelithiasis, pyelonephritis and intestinal and peritoneal tuberculosis.

Treatment.—The treatment is always surgical exploration of the abdomen when the symptoms are acute. Simple exploration seems to do no harm in these cases, and often has a beneficial effect whether or not any further procedure is done (Ungar; Bell). Surgical opinion varies as to the advisability of removing or leaving the enlarged mesenteric nodes, as both procedures have been successful (Head; Bell). Newbolt recorded an instance, however, when failure to remove the largest nodes necessitated a secondary laparotomy to remove them before relief of symptoms was obtained. More radical measures are seldom necessary, although a few cases are reported in which abscessed nodes were scraped out (Gehrels) or ileotransversostomy or intestinal resection was performed (Strömbeck).

Complications.—The disease process may result in diverse complications originating from the primary disease of the lymph nodes.

Calcification of nodes overlying the ureters may result in compression of the ureter with symptoms of disease of the urinary tract such as hematuria, frequent and painful micturition and abdominal pain simulating ureteral colic (Schmieden; Walker; Davidovitch; Golden and Reeves). The acute process sometimes results in the perforation and rupture of a caseous gland (Floderus; Edén; Iselin; Head; Bagg; Bell; Grimm), intestinal obstruction (Floderus; Jones; Brüning; Homuth; Wakely; Head; Gutzeit; Koschucharoff; Hubrich; Mischel), compression of the pylorus or duodenum (Floderus; Keppler and Erkes; Matyas; Orth; Wantoch), acute ileus (Floderus; Carson; Homuth), intra-abdominal abscess (Edén; Iselin; Head; Bagg), hydronephrosis (Hepburn; Valentin), obstruction of the biliary ducts (Floderus; Jean), obstruction of the portal vein with associated ascites (Floderus), erosive bleeding from large intra-abdominal vessels (Whitworth; Ruescher; Rawitzkaja; Fischmann), and thrombosis in the mesenteric vessels (Murray).

Mechanism of Infection.—The exact mechanism by which the mesenteric lymph nodes become infected with tuberculosis has not been demonstrated. The tuberculous intestinal tract has been the most obvious source of infection. The digestive tract has also been considered as the probable route through which tubercle bacilli in infected foods have been transmitted to the mesenteric lymph nodes. Infected sputum and milk have been most commonly accused as vehicles in the transmission of the organisms to the gastro-intestinal tract and to the lymph nodes of the mesentery (Branson; Braithewaite; Head). It is stated that tuberculosis of the intestinal tract is rare in the first years of life, after which it increases in frequency to the fourth or fifth years (Opie). It has been pointed out that the increase in the number of gastro-intestinal infections is coincident with the average time of weaning, and that this is probably due to a change in diet through which contaminated foods may invade the intestinal tract. This theory of infection of the digestive tract with relation to the age period is of significance in considering the sources and routes of infection of the mesenteric lymph nodes.

Intestinal stasis associated with distention and catarrhal inflammation with abrasions of the mucous membrane have been mentioned as producing portals of entry to the mesenteric lymph nodes (Bell). It has been suggested that the resistance of the mucosa is lessened by the absorption of intestinal toxins, thus permitting the passage of organisms (Thiemann; Carson). Others believe that organisms may pass through the intact mucosa (Walsham; Morley; Philip). The latter view is not generally accepted. Trauma and intestinal parasites have also been considered as etiologic factors (Bell; Wagner). The constant involvement of nodes draining the region of the appendix has frequently sug-

gested tuberculosis of that organ. Although tuberculosis of the appendix occurs in from 2 to 5 per cent of abnormal appendixes (Lennander and Nyström), no clear case with associated mesenteric lymphadenitis has been recorded. Recent investigations indicating that tubercle bacillemia may be present shortly after the onset of a tuberculous infection any place in the body favor a hematogenous route of infection (Sata; Löwenstein, 1930 and 1931).

Pathology.—The pathologic process in the tuberculous mesenteric lymph node does not deviate from its usual manifestations; thus, the findings are dependent on the stage of the disease. The progress of the condition is probably governed by the virulence of the organism and the resistance of the individual subject.

The principal lesions noted at operation are: enlarged, inflamed, discrete nodes; masses of nodes grouped around a central suppurative or caseous node, or small, scattered, calcified glands (Braithewaite; Bell). In the later stages of softening, caseation, calcification and formation of scars, the disease condition is easy to recognize, and it is usually not confused with any other. In early stages, however, its gross recognition is difficult, and consequently requires microscopic examination or inoculation of guinea-pigs with the tissue for its decisive identification. The importance of the inoculation of guinea-pigs as a final diagnostic measure, after gross and histologic examination of the tissue, is emphasized by the experimental work of MacFadyen and MacConkey and of Bartel. Mesenteric lymph nodes showed, in these studies, the presence of tubercle bacilli in 25 per cent of a series of nontuberculous cases brought to autopsy, in which the lymph nodes appeared normal on gross and histologic examination, and in which there was neither clinical nor autopsy suggestion of tuberculosis elsewhere in the body.

Tuberculous mesenteric lymphadenitis most frequently affects the nodes which drain the ileocecal region (Corner, 1905; Braithewaite). Almost any node or group of nodes within the mesentery of the small intestine may be involved, however, because of their close anatomic relationships. In many instances the disease may be localized in the primary group of nodes at the margin of the intestine or at the root of the mesentery. Frequently the pathologic process is confined to the ileocecal group of nodes. In practically every instance the disease involves the nodes along the ileocolic artery to some extent (fig. 2).

Causation of Pain.—The symptoms of pain, spasmodic mild abdominal distress, nausea, emesis and diarrhea can probably be explained as being due to acute alterations in and about the mesenteric nodes. Wilms and Kappis showed that sensations of pain can be elicited within a field extending from the root of the mesentery to its free border, especially along the vessels. The mesenteric nodes are situated

chiefly along the vessels, and consequently stretching of the peritoneum from acute swelling and scarification or, later, calcification of the nodes

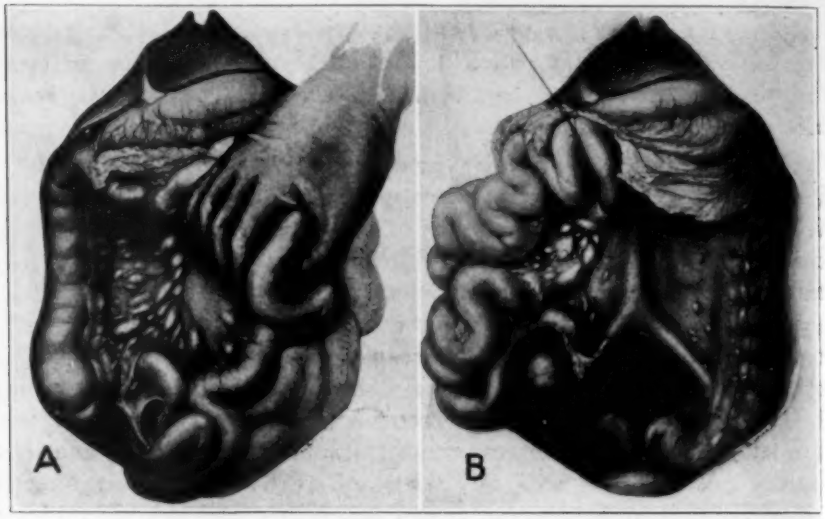

Fig. 2.—*A*, enlarged, discrete lymph nodes similar to the kind often noted at operation. The right side of the mesentery is exposed, and the location of the enlarged nodes along the course of the larger blood vessels is well shown. *B*, enlarged, discrete lymph nodes when seen from the left side of the mesentery. From L. P. Bell (Surg., Gynec. & Obst. **45**:465, 1927).

Fig. 3.—A calcified lymph node with associated puckering and scarification of the overlying peritoneum. It is evident that calcified spicules are also present, which might project into and irritate the surrounding peritoneum. From L. P. Bell (Surg., Gynec. & Obst. **45**:465, 1927).

involving the overlying peritoneum (fig. 3) could easily be considered as causative factors in the production of painful sensation (Valentin;

Braithewaite; Davidovitch; Golden and Reeves; Auchincloss). Colic-like pains have been ascribed to intestinal spasms and partial invaginations (Carson; Gray; Braithewaite).

Prognosis.—The prognosis of mesenteric lymphadenitis with regard to freedom from symptoms is fair. Strömbeck observed fifty-five patients after operative exploration over a period of from six to twelve years, thirty (55 per cent) of whom were free from symptoms. The early literature shows a high mortality in mesenteric lymphadenitis, for in a series of fifteen operative cases Floderus had a mortality of 33 per cent. Recent reports of larger series of cases, however, showed no operative mortality (Bagg; Strömbeck).

NONTUBERCULOUS MESENTERIC LYMPHADENITIS

The literature regarding mesenteric lymphadenitis referred almost exclusively to the tuberculous type until 1920. Apparently it had been considered unlikely that the condition might be derived from some other infectious organism. Differentiation of the nontuberculous from the tuberculous type has not been entirely satisfactory, and has been based principally on pathologic and bacteriologic studies. The more recent recognition of nontuberculous enlargement of the mesenteric lymph nodes has led to its clinical classification as a distinct entity. Anderson directed attention to the fact that enlargement of the mesenteric lymph nodes had caused confusion with appendicitis. Wilensky, in 1920, wrote concerning a group of frequently encountered cases in which symptoms of acute abdominal abnormality are presented but in which on exploration only enlarged mesenteric lymph nodes are found. Histologic and bacteriologic study of the enlarged nodes fails to show tuberculosis, but shows simple lymphoid hyperplasia and pyogenic organisms. Pathologically and bacteriologically the processes are pyogenic. Clinically the condition cannot be demarcated from tuberculous mesenteric lymphadenitis, nor from acute appendicitis.

The following description is that of a case of nontuberculous mesenteric lymphadenitis encountered in the surgical service of the University of Minnesota Hospital.

History.—A white girl, 9 years of age, was admitted to the University of Minnesota Hospital on July 16, 1925 and was discharged on July 29. The child was well until approximately one year before admission. At this time she began to complain of intermittent, dull pain somewhat localized in the epigastrium. The appetite remained good, however, and there had been no nausea, emesis, diarrhea or constipation. The mother thought that the child had a fever at times, but no temperatures had been recorded.

Two days before admission to the hospital the patient was seen by a physician because of marked abdominal pain. At this time the temperature was 100 F. A diagnosis was made of acute appendicitis, and the child was removed to the University of Minnesota Hospital for care.

The history showed that the child had complained for three years of intermittent urinary frequency and burning. She had pneumonia twice and influenza on one occasion. The family history was irrelevant.

Physical Examination.—The child appeared to be well developed and well nourished. The pulse rate was 110 and the temperature 99.8 F. The remainder of the examination revealed no abnormality except in the abdomen, where tenderness was present on palpation in the right lower quadrant, without muscle spasm or rigidity. Rectal examination revealed more tenderness on the right than on the left. No lymphadenopathy or abdominal masses were noted.

Laboratory Data.—The urine was normal except for a few epithelial and white blood cells; the hemoglobin was 72 per cent, and the white blood cell count 17,250, with a differential count of polymorphonuclear neutrophils 72 per cent and lymphocytes 28 per cent.

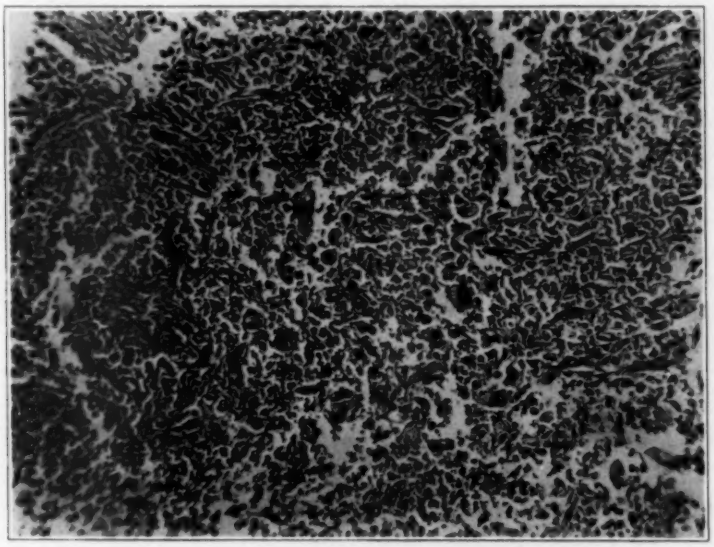

Fig. 4.—A photomicrograph of a section of the lymph node removed at operation in the case of nontuberculous mesenteric lymphadenitis. Simple lymphoid hyperplasia is shown; × 100.

Diagnosis and Therapy.—In view of the urinary history a diagnosis of pyelitis was strongly considered. Appendical involvement could not be ruled out, however, and exploratory laparotomy was performed. The appendix appeared to be normal by gross examination, but marked adenopathy was noted throughout the entire mesentery. The appendix and one of the enlarged nodes were removed for histologic examination. Microscopic examination of the appendix revealed no abnormalities, and study of the lymph node showed simple lymphoid hyperplasia (fig. 4). The final diagnosis was nontuberculous mesenteric lymphadenitis.

Postoperative Course.—The child's postoperative convalescence was uneventful. Observers in the University of Minnesota outpatient dispensary noted three years later that the child had had no exacerbations of symptoms. Roentgen examination of the abdomen showed no calcified mesenteric lymph nodes, and reaction to the Mantoux test was negative.

Frequency.—Publications dealing with the condition as an entity are relatively few, and consequently the frequency of occurrence of the condition has not been widely studied. The disease is thought to be common, but unrecognized (Struthers; Freeman; Heusser; Wilensky and Hahn; Short). Its incidence has been determined in one series of two hundred laparotomies, in which it was found to occur in 6 per cent of the cases (Short). This would indicate a much greater frequency than of tuberculous mesenteric lymphadenitis.

Age.—Nontuberculous mesenteric lymphadenitis is essentially a disease of children, the age period ranging from birth to 15 years (Wilensky; Struthers; Freeman; Short). The condition has been recorded in young adults, but is far more common in the preadolescent period (Struthers). Heusser, Guleke and Sennels presented reports of more than two hundred cases of mesenteric lymph node hyperplasia, occurring chiefly in patients between the ages of 10 and 20 years.

Symptomatology.—It is stated that nontuberculous mesenteric lymphadenitis may simulate any acute abdominal condition for which laparotomy is commonly performed (McFadden). The condition assumes both acute and chronic forms (Wilensky; Struthers; Freeman; Wilensky and Hahn; Short). The symptoms in the acute type simulate those of acute appendicitis so closely that they cannot be differentiated. The patient usually complains of sudden, crampy, colicky, abdominal pain, which is first diffuse about the umbilical region, later localizing in the right lower quadrant of the abdomen, or just to the right of the umbilicus. The pain commonly ceases as suddenly as it began, and is recurrent. There may be associated nausea and emesis, constipation or diarrhea. In the chronic form there is commonly a history of a long period of loss of energy and weight with associated fleeting gastric and abdominal distress, and finally a suddenly precipitated acute abdominal pain.

Physical Findings.—Physical examination generally shows a definite area of abdominal tenderness, cutaneous hyperesthesia, muscle spasm and rigidity over the tender area, and often rebound tenderness. Usually no masses are palpated, and results of a rectal examination are negative. The pulse rate is slightly increased, and the temperature varies from 99 to 104 F. (Freeman; McFadden).

Laboratory Data.—Results of laboratory examination are usually negative except for a white blood cell count which usually varies from 12,000 to 17,000, 80 per cent of the cells being polymorphonuclear neutrophils.

Diagnosis.—The condition must be differentiated from the acute abdominal processes common to childhood such as Meckel's diverticulitis, intussusception and pyelonephritis. Nontuberculous lymphadenitis

is almost invariably confused with acute appendicitis, and fails to present any characteristic symptoms which will justify a clinical differentiation of the two conditions.

Treatment.—Surgical exploration of the abdomen is the usual treatment of the condition (Wilensky; Struthers; Freeman; Heusser; Wilensky and Hahn; McFadden; Short). There is no unanimity of opinion as to the advisability of excision of the enlarged lymph nodes. In most of the reported cases the nodes have not been disturbed. It is unanimously agreed that the appendix should be removed whether or not it shows a gross pathologic process. Opening the abdomen seems to be efficacious treatment, for in most instances an uneventful recovery ensues.

Complications.—Intestinal obstruction and fecal fistulas have been the principal complications associated with nontuberculous lymphadenitis (Wilensky). Both types are rare.

Mechanism of Infection.—The mechanism of infection is unknown. Catarrhal conditions and ulcerations of the mucosa have been considered as possible portals of entry for the invading organisms (Freeman; Wilensky and Hahn). Contaminated food and milk have been described as vehicles of infection (Freeman). Intestinal parasites and trauma have been mentioned as possible predisposing factors (Heusser; Wagner). The appendix has been suggested as the most likely portal of entry for the infection (Wilensky). The fact that enlarged mesenteric lymph nodes are not seen in acute appendicitis, and that the appendix is normal in cases of nontuberculous mesenteric lymphadenitis, is thought to be strong contradictory evidence regarding this theory. It is generally agreed that pyogenic organisms are the principal etiologic factors in nontuberculous mesenteric lymphadenitis (Wilensky; Struthers; Freeman; Wilensky and Hahn). This agreement is based on pathologic and bacteriologic studies. The absence of tubercle bacilli has been demonstrated by cultural and antiformin methods and by the inoculation of guinea-pigs (Heusser).

Pathology.—The gross appearance of the nodes when seen at operation is somewhat variable (Wilensky; Struthers; Freeman; Wilensky and Hahn; Bell; Short). The early stages of the process consist essentially of enlargement of the affected nodes, which are usually discrete and dull red. The surrounding peritoneum appears to be normal. Early caseation appears as single or multiple small yellow spots on the surface of the reddened node. With this change the surrounding peritoneum shows an extension of the inflammatory process. There may be an increase of peritoneal fluid at this time. The caseation may progress to form a definite abscess of the node or nodes involved. The abscess is usually well walled off, however, but may become extremely

large. Finally, the process may recede and result in a condition of scarification or cicatrization of an area of peritoneum about the previously diseased gland. The final stage of the process is calcification, wherein a hard node is formed possessing multiple spicules which project into and irritate the surrounding peritoneum.

The affected nodes may be scattered through the mesentery. They are usually most prominent, however, along the ileocolic artery or at

TABLE 1.—*A Comparison of the Salient Clinical and Pathologic Features of Tuberculous and Nontuberculous Mesenteric Lymphadenitis*

	Tuberculous	Nontuberculous
Frequency	In general autopsy statistics, 1 to 3% In abdominal laparotomies, 0.74% In autopsies on tuberculous cases, 0.79%	In abdominal laparotomies, 6%
Age	Birth to 15 years	Birth to 15 years
Symptoms	Acute, or chronic which became acute; pain: sudden onset, colicky, intermittent, first generalized or about umbilicus, later localizing in right lower quadrant of abdomen; nausea and emesis	The same
Physical findings	Abdominal tenderness; muscle spasm and rigidity; shock en retour; pulse rate, 100 to 120; temperature, 100 to 104 F.; often a positive Pirquet reaction	The same
Laboratory observations	Leukocytosis, 12,000 to 17,000; 80% polymorphonuclear neutrophils	The same
Treatment	Surgical exploration, with or without removal of nodes equally successful, and appendectomy	The same
Complications	Urinary symptoms due to calcified epiureteral nodes; abscess and perforation of abscess; intestinal obstruction; acute ileus; hydronephrosis; obstruction of common bile duct or portal vein	The same
Etiology	Tubercle bacilli	Pyogenic or unknown organisms
Source and mechanism of infection	Tuberculosis of digestive tract; infected milk or sputum; organisms passing through normal or eroded bowel wall; tuberculosis of the appendix	Infected milk, sputum, food; diseased appendix; intestinal parasites and trauma as predisposing factors
Pathology	Enlarged, inflamed, discrete nodes; masses of nodes about a central caseous or suppurative node; calcified nodes; scarified peritoneum	The same
Pathologic anatomy	Nodes draining ileocecal region; any place in mesentery, along ileocolic artery	Nodes along ileocolic artery, scattered, along root of mesentery
Prognosis	55 per cent five year cures	87 per cent four year cures

the root of the mesentery. Microscopic examination of the nodes shows only lymphoid hyperplasia.

Prognosis.—Strömbeck followed up forty cases for an average of 3.9 years postoperatively and found 87 per cent free from symptoms. The operative procedure had consisted simply of appendectomy. There was no operative mortality.

A comparison of the preceding data, concerning tuberculous and nontuberculous mesenteric lymphadenitis, indicates many points of similarity (table 1). Several writers consider that the tubercle bacillus

must be strongly suspected of being the infectious organism in all cases of lymphadenitis in the mesentery (Clute; Struthers; Guleke; Bell; McFadden). In fact, the age period in which the disease occurs, the symptomatology, physical findings, laboratory data, etiology, pathology and pathogenic anatomy are so similar that one strongly suspects that the two conditions are simply slight variations of a fundamental disease process.

PRIOR INVESTIGATIONS OF MESENTERIC LYMPH NODES

Repeated contact with tuberculous and nontuberculous mesenteric lymphadenitis in the surgical service of the University of Minnesota Hospital led Dr. O. H. Wangensteen to suggest an investigation of the fundamental aspects of the condition. In the preceding survey it is evident that the subject of mesenteric lymphadenitis has evoked considerable clinical interest. Its extent may be measured by the fact that Strömbeck (1932) wrote a monograph of about two hundred and fifty pages regarding a clinical investigation of the condition. He realized, however, the futility of many clinical observations and publications, and thoroughly summed up their deficiencies when he stated: "There are as yet no certain measures of the normal variation of the mesenteric lymph glands. Therefore, the possibility cannot be excluded that in many of the published cases the size of the glands was within normal limits, and that the symptoms were caused by factors which could not be observed objectively." It is this most fundamental factor with which the present study is concerned.

Historic Data.—The development of knowledge concerning the lymphatic system has resulted from the studies of widely scattered investigators. The writings of Herophilus are credited with vague references to the lacteal vessels, but the earliest specific knowledge of them was recorded by the Italian, Aselli, in 1627. The Frenchman, Pecquet, in 1651, noticed white fluid in the heart of a dog, and traced it back to the subclavian vein and the thoracic duct. The Swedish investigator, Rudbeck, in 1653, followed the chyle back to the lymph vessels of the mesentery. The Dutchman, Swammerdam, in 1664, discovered the lymphatic valves.

Physiologic studies regarding the lymphatic system progressed more slowly. William and John Hunter, in the eighteenth century, upheld the lymphatic system as the sole absorptive element in the body. Magendie, however, in 1825, showed that the venous radicals were also absorptive structures, and in 1850, Ludwig demonstrated the formation of lymph by the diffusion of fluid from the capillary bed.

Detailed knowledge of the lymph node system has fallen behind that of the lymph vascular system. Bertein and Worms credited Sydenham with the first description of enlargement of the mesenteric lymph nodes

in children. Monro (1760), however, was the first writer to mention swelling of the lymph nodes in the head, axillae and inguinal regions. Hodgkin is said to have been the first, in 1832, to recognize the possibility of lymph nodes being the seat of specific diseases. Werner and Feller, in 1784, however, described an atrophy and hardening of the mesenteric lymph nodes which they thought to be due to tuberculosis.

Knowledge concerning limited portions of the general lymphatic system, such as the lymphatic nodes of the intestinal mesentery, also originated with the early investigators. Aselli found an extensive organization of the mesenteric lymph nodes in dogs. This investigation resulted in the naming of these nodes the pancreas of Aselli.

Mascagni, by 1787, apparently possessed a fairly extensive conception of the mesenteric lymph nodes. He described their shape, and was cognizant of a disease which hardened and atrophied them. He stated that these nodes in children become organized into groups with advancing growth of the body. He believed that the growth of the mesenteric lymph nodes was closely related to the growth of the body, but that in middle life they began to diminish and gradually disappeared.

Cruikshank, in 1786, considered the number of mesenteric nodes to vary from 130 to 150, and he noted a disappearance of some of the nodes in older persons. He stated that they varied in size from $\frac{1}{20}$ to $\frac{1}{8}$ inch (0.12 to 0.32 cm.) in diameter. This observation seems to be the first quantitative description of their size. Later writers were more interested in the pathologic conditions affecting the nodes. The only quantitative data recorded by them related to the number of mesenteric lymph nodes.

In 1889, Wullenweber undertook the first quantitative study of the size of mesenteric and mesocolic lymph nodes under normal and pathologic conditions. His method consisted essentially of excision of the nodes and of weighing them in groups of 10, 20 or 50 nodes, from which he obtained an average weight for each of the groups. He did not pretend that his method was particularly accurate, but felt that it offered a better measure of the size of the lymph nodes than had yet been obtained. He found the total number of abdominal lymph nodes to vary from 154 to 540 in a series of seventeen patients ranging in age from birth to 52 years. The variation in weight of these nodes was extreme, ranging from 0.0002 to 3.22 Gm. The mesenteric lymph nodes were examined separately in only four patients, ranging from 11 to 68 years of age. The number in these cases varied from 113 to 437, and the average weight of the lymph nodes varied from a minimal of 0.002 to 3.22 Gm. The average weight of the entire group of mesenteric lymph nodes in these cases varied from 0.025 to 0.044 Gm. He concluded from his study of this group of cases that there was a distinct growth in the lymph nodes of the mesentery and abdomen which paralleled general

bodily development, and that with increasing age after the developmental period a decrease in the size of the nodes takes place. It would seem, however, that the results of this investigation hardly merit such a sweeping conclusion, because of the few cases studied.

Anatomy.—The following description by Delamere, Porier and Cuneo shows the regional lymph nodes dealt with in the present investigation:

> The lymphatics of the cecum and appendix are much more developed than those of other segments of the intestine. There are a few small nodes on the anterior and posterior surfaces of the cecum which terminate in a fairly large group of nodes (5 or 6) at the termination of the ileocecal artery. The appendical glands are essentially the same group, although there may be interposed in their route a few nodules in the retroileal meso-appendix.
>
> The lymphatics of the small intestine form two systems relatively independent of one another draining the mucosal and muscular layers of the intestinal walls. The glands in the mesentery into which the collecting trunks empty appear at first glance to be scattered indiscriminately through the mesentery. They are, however, arranged in a fairly definite plan and may be divided into three groups. A primary group is present placed in the terminal arterioles arising from the last anastomotic arch. A second group is present in the course of the primary superior mesenteric branches at the level of the first anastomotic arch. These glands are larger than the primary group. A third group may be found around the trunk of the superior mesenteric artery at its commencement. The glands are most numerous in the jejunal mesentery, diminishing progressively in number to the terminal ileum.

QUANTITATIVE STUDY OF MESENTERIC NODES

The aim of this investigation has been to determine the normal weight of mesenteric lymph nodes in children. Such a study seemed so beset by uncontrollable factors and inaccuracies of observation that the results would probably be of little value; nevertheless, the entire clinical entity built around apparent enlargement of the mesenteric lymph nodes would remain largely hypothetic unless some determination of the normal was made for purposes of comparison. Consequently, an attempt has been made to establish a concept of the normal size of these nodes. The problem has been attacked without the influence of preconceived ideas, and the many variable factors affecting such an undertaking have been faithfully recorded in order that any reader may judge for himself as to their significance.

Material.—It was proposed to study the size of the mesenteric lymph nodes in infants and children from birth to 15 years of age. This period of life was chosen arbitrarily in order that the investigation might be closely linked to the clinical entity of mesenteric lymphadenitis, wherein both the tuberculous and the nontuberculous types are encountered during this age period.

Arrangements were made with the pathology departments of the University of Minnesota, Minnesota General Hospital, Minneapolis General Hospital and Ancker (St. Paul City and County) Hospital, whereby autopsy specimens from children within the desired age group were obtained. The various pathologists and their

assistants in these institutions gave hearty cooperation in the collection of this material.

Specimens chosen for study consisted of mesenteries from premature and full-term stillborn infants, in whose cases there had been no history of recent maternal infection, and in whom the pathologist had found no evidence of a disease process related to the gastro-intestinal tract. Mesenteries fulfilling these requirements were obtained without great difficulty, because of the large number of autopsies performed on stillborn infants in the department of pathology at the University of Minnesota.

Considerable difficulty was encountered, however, in the collection of adequate material during infancy and childhood. Death from accidental causes was thought to preclude to some extent the possibility of recent infections affecting the mesenteric nodes, and consequently the material was limited, at first, to cases in which the cause of death had been accidental. No such cases were obtained, in spite of cooperative pathologists, because apparently children dying from this cause are seldom subjected to a postmortem examination. Furthermore, it was soon evident that there was not only an extreme scarcity of traumatic accident material, but that autopsies on children more than 2 years of age were infrequent.

My views necessarily broadened, and it was felt that specimens from almost any patient dying in childhood would be acceptable except those with diseases of the reticulo-endothelial system. This conversion was influenced by the obvious fact that no mesenteric nodes after birth would be exempt from the effects of organisms or toxins derived from the gastro-intestinal tract. In other words, no absolutely uncontaminated or completely normal lymph node system would be encountered. Furthermore, the effects of the various causes of death on the size of the nodes could not be evaluated, for no normal size of lymph nodes had been determined. It was concluded that the investigation must commence somewhere, and its results evaluated with due regard for many possible influential factors.

The material examined consisted of fifty cases occurring in children aged from 1.5 months prematurity to 12 years (table 2). The study included mesenteries from thirteen premature infants, five full-term infants, ten infants less than 1 month old, ten infants ranging from 1 to 6 months of age, two infants between 6 months and 1 year, three children between 1 and 2 years, one child of 4 years, two children between 5 and 6 years, three children of 8 years and one child 12 years of age. The sex distribution was fairly even, there being twenty-two female and twenty-eight male infants and children examined. The various causes of death included prematurity, anencephaly, cerebral hemorrhage, hydrocephalus and spina bifida, hydrops foetalis, strangulated hernia and peritonitis, congenital heart disease, pneumonia, meningitis, otitis media, mastoiditis, pertussis, intussusception, congenital syphilis, dysentery, abscess of the lungs, septicemia, rectovaginal fistula, pericarditis, third degree burns, rheumatic heart disease, poliomyelitis and abscess of the brain.

Methods.—The specimens received from the various pathologists consisted of the entire mesentery of the small intestine extending from the duodenojejunal juncture to the cecum. The mesentery had been cut across at its attachment to the posterior body wall, thus including in each specimen a portion of the superior mesenteric artery proper. The intestinal tract was present in the peripheral margin of the mesentery. The vermiform process and cecum were preserved in each instance, in order that the proximal or distal portions of the mesentery might be more easily identified. All specimens were immediately placed in formaldehyde U. S. P. (1:10), which was the standard fixative solution used in the various hospitals and pathologic laboratories.

TABLE 2.—*Summary of Observations on Fifty Subjects*

Case	Age*	Sex	Cause of Death	Jejunal Region		Ileal Region		Mesenteric Root Region		Total Mesenteric Lymphoid Tissue		
				No. of Nodes	Average Weight, Gm.	No. of Nodes	Average Weight, Gm.	No. of Nodes	Average Weight, Gm.	No. of Nodes	Average Weight, Gm.	Total Weight, Gm.
1	Prem. 4½ mo.	F	Prematurity	27	0.0006	13	0.0007	7	0.0071	47	0.0016	0.0758
2	Prem. 4½ mo.	M	Prematurity	31	0.0005	9	0.0014	8	0.0021	48	0.0009	0.0475
3	Prem. 6 mo.	F	Prematurity	53	0.0017	34	0.0019	20	0.0069	107	0.0028	0.2981
4	Prem. 7 mo.	M	Prematurity	68	0.0062	34	0.0048	10	0.0609	112	0.0107	1.1952
5	Prem. 7 mo.	F	Prematurity	12	0.0020	11	0.0030	9	0.0074	32	0.0039	0.1251
6	Prem. 7 mo.	M	Prematurity	74	0.0001	22	0.0002	11	0.0011	107	0.0002	0.0298
7	Prem. 7 mo.	F	Prematurity	66	0.0008	42	0.0019	29	0.0107	137	0.0033	0.4520
8	Prem. 7 mo.	M	Prematurity	52	0.0009	29	0.0008	9	0.0096	90	0.0017	0.1618
9	Prem. 7 mo.	F	Prematurity	12	0.0014	3	0.0062	11	0.0101	26	0.0049	0.1291
10	Prem. 8 mo.	M	Prematurity	56	0.0004	29	0.0003	20	0.0029	105	0.0008	0.0913
11	Prem. 8 mo.	M	Prematurity	49	0.0019	20	0.0028	16	0.0112	85	0.0039	0.3328
12	Prem. 8 mo.	F	Anencephalic	119	0.0015	53	0.0015	23	0.0076	195	0.0022	0.4377
13	Prem. 8 mo.	M	Prematurity	61	0.0036	20	0.0049	0	0.0000	81	0.0039	0.3207
14	S. B. F. T.	M	Cerebral hemorrhage	37	0.0016	46	0.0036	21	0.0243	104	0.0071	0.7468
15	S. B. F. T.	M	Prematurity	58	0.0048	32	0.0066	28	0.0356	118	0.0126	1.4899
16	S. B. F. T.	F	Spina bifida; hydrocephalus	203	0.0031	75	0.0026	11	0.0204	289	0.0036	1.0560
17	S. B. F. T.	M	Prematurity	46	0.0065	70	0.0010	16	0.0218	112	0.0062	0.6996
18	S. B. F. T.	F	Prematurity	28	0.0041	16	0.0085	18	0.0305	62	0.0129	0.8003
19	1 day	M	Prematurity	33	0.0025	33	0.0016	6	0.0075	72	0.0025	0.1800
20	1 day	F	Hydrops foetalis	84	0.0004	42	0.0018	11	0.0188	137	0.0023	0.3199
21	7 days	M	Strangulated hernia; peritonitis	105	0.0061	84	0.0051	26	0.0230	215	0.0077	1.6721
22	10 days	M	Congenital heart disease	56	0.0049	38	0.0053	9	0.0293	103	0.0072	0.7409
23	11 days	F	Bronchopneumonia	60	0.0021	27	0.0028	19	0.0190	106	0.0055	0.5786
24	12 days	M	Pneumonia	111	0.0045	69	0.0063	10	0.0519	190	0.0077	1.4555
25	13 days	M	Meningitis	30	0.0129	8	0.0191	2	0.1070	40	0.0189	0.7551
26	13 days	M	Mastoiditis; bronchopneumonia	37	0.0103	27	0.0014	20	0.0755	84	0.0229	1.9290
27	13 days	M	Otitis media	78	0.0030	37	0.0071	16	0.0221	131	0.0065	0.8536
28	17 days	F	Mastoiditis; bronchopneumonia	117	0.0042	118	0.0036	31	0.0203	266	0.0058	1.5451
29	37 days	M	Pneumonia	27	0.0165	16	0.0163	14	0.1551	57	0.0505	2.8785
30	2 mos.	F	Rheumatic heart disease	97	0.0049	63	0.0042	19	0.0300	179	0.0073	1.3008
31	3 mos.	M	Mastoiditis; lobar pneumonia	48	0.0057	13	0.0059	0	0.0000	61	0.0058	0.3527
32	3 mos.	M	Pertussis	42	0.0109	51	0.0061	11	0.0393	104	0.0116	1.2029
33	4 mos.	M	Hydrocephalus	68	0.0065	37	0.0027	28	0.0257	133	0.0095	1.2667
34	4½ mos.	M	Congenital heart disease	41	0.0035	57	0.0020	19	0.0391	117	0.0086	1.0009
35	5 mos.	M	Mastoiditis	33	0.0065	21	0.0095	22	0.0373	76	0.0162	1.2375
36	5 mos.	F	Otitis media	42	0.0182	17	0.0322	17	0.2150	76	0.0653	4.9656
37	5 mos.	F	Intussusception	62	0.0129	10	0.0230	15	0.1166	87	0.0319	2.7801
38	6 mos.	F	Congenital syphilis	91	0.0048	81	0.0046	37	0.0192	209	0.0073	1.5241
39	9 mos.	F	Dysentery	29	0.0247	26	0.0259	20	0.1851	75	0.0691	5.1813
40	11 mos.	M	Meningococcic meningitis	49	0.0319	30	0.0386	15	0.2006	94	0.0610	5.7341
41	13 mos.	F	Bronchopneumonia	65	0.0132	62	0.0057	16	0.0402	143	0.0129	1.8505
42	18 mos.	M	Abscess of lung	46	0.0227	52	0.0239	11	0.1336	109	0.0344	3.7595
43	2 yrs.	F	Septicemia	121	0.0177	72	0.0128	38	0.2321	231	0.0514	11.8854
44	4 yrs.	F	Rectovaginal fistula	59	0.0605	63	0.0546	24	0.1113	146	0.0663	9.6849
45	5 yrs.	M	Pericarditis	106	0.0175	104	0.0263	2	0.0635	212	0.0222	4.7179
46	6 yrs.	F	Third degree burns	15	0.0841	8	0.0188	34	0.3115	57	0.2095	11.9389
47	8 yrs.	F	Rheumatic endocarditis	55	0.0136	45	0.0197	24	0.2782	124	0.0670	8.3115
48	8 yrs.	M	Lobar pneumonia	157	0.0167	68	0.0197	39	0.1448	262	0.0365	9.5647
49	8 yrs.	F	Poliomyelitis	71	0.0064	36	0.1297	9	0.8409	116	0.1608	18.6540
50	12 yrs.	M	Abscess of the brain	91	0.0321	40	0.0504	8	0.9564	139	0.0932	12.9538

* Prem. means premature, S. B., stillborn, and F. T., full-term.

The effect of formaldehyde in various strengths on the mesenteric lymphoid tissues was carefully considered. Six lymph nodes from the mesentery of a stillborn full-term infant were dissected free and weighed individually. Two of these nodes were then placed in a 5 per cent solution of formaldehyde, 2 in a 10 per cent solution and 2 in a 15 per cent solution. The weight of the nodes in each solution was then recorded daily for a time, later it was recorded every other day, and as soon as the change in weight became less rapid records were made at weekly intervals. These observations showed an immediate increase in the weight of the nodes, the greatest increase taking place in the nodes placed in the 5 per cent solution and the least increase in the lymphoid tissue placed in the 15 per cent solution (table 3). The rapid increase in weight was followed by a fairly rapid and steady decrease in the weight of the nodes in each fixative solution. Finally, the loss of weight ceased, and it was noted that the lymphoid tissue

TABLE 3.—*Changes in Weight of Mesenteric Lymph Nodes During Fixation (Gm.)*

	5% Formaldehyde		10% Formaldehyde		15% Formaldehyde	
Date	A	B	C	D	E	F
2/25/31	0.2364	0.2527	0.1874	0.1931	0.1542	0.1362
2/26/31	0.2360	0.2530	0.1950	0.1968	0.1556	0.1394
2/27/31	0.2341	0.2524	0.1946	0.1962	0.1541	0.1364
2/28/31	0.2324	0.2519	0.1901	0.1910	0.1522	0.1347
3/ 1/31	0.2308	0.2510	0.1880	0.1880	0.1500	0.1324
3/ 2/31	0.2296	0.2484	0.1872	0.1864	0.1498	0.1309
3/ 3/31	0.2274	0.2461	0.1857	0.1860	0.1509	0.1287
3/ 4/31	0.2269	0.2460	0.1842	0.1871	0.1500	0.1277
3/ 5/31	0.2266	0.2454	0.1836	0.1870	0.1492	0.1261
3/ 6/31	0.2251	0.2447	0.1824	0.1864	0.1472	0.1260
3/ 7/31	0.2244	0.2449	0.1819	0.1845	0.1451	0.1247
3/ 8/31	0.2230	0.2440	0.1781	0.1796	0.1429	0.1244
3/10/31	0.2227	0.2438	0.1760	0.1745	0.1417	0.1241
3/12/31	0.2222	0.2435	0.1751	0.1740	0.1416	0.1241
3/14/31	0.2216	0.2432	0.1739	0.1738	0.1414	0.1240
3/16/31	0.2212	0.2428	0.1722	0.1731	0.1411	0.1237
3/18/31	0.2200	0.2426	0.1704	0.1714	0.1409	0.1239
3/20/31	0.2206	0.2421	0.1678	0.1709	0.1409	0.1237
3/27/31	0.2205	0.2420	0.1641	0.1696	0.1408	0.1234
4/ 3/31	0.2202	0.2419	0.1620	0.1662	0.1407	0.1232
4/10/31	0.2200	0.2416	0.1600	0.1650	0.1407	0.1231
4/17/31	0.2200	0.2415	0.1590	0.1651	0.1407	0.1230
4/24/31	0.2200	0.2416	0.1590	0.1650	0.1407	0.1231
			Weights Unfixed, Gm.			
2/23/31	0.1700	0.1801	0.1590	0.1650	0.1370	0.1172

placed in the 10 per cent solution of formaldehyde had returned to its original weight. The specimens of tissue placed in the 5 and 15 per cent solution failed to return to their original weights. The 10 per cent solution of formaldehyde, therefore, was concluded to be the most desirable fixative, as no corrective factor need be used. The mesenteric lymph node tissue returned to its original nonfixed weight after a period of approximately two months, following which there was no appreciable change in weight. Consequently, all specimens were fixed in a 10 per cent solution of formaldehyde for a period of 2.5 months before being studied.

The individual lymph nodes were dissected free from the mesenteric fat, areolar tissue and peritoneum with sharp dissecting scissors. The smallest mesenteric nodes (0.0001 Gm.) could be seen with the naked eye if the mesentery was held up to a strong light and transilluminated. The dissections were made easier by using an ophthalmologic loupe, by means of which the details of the tissue were magnified and consequently better visualized. Dissection of nodes of all sizes showed that they could easily be freed from the surrounding tissues. Fixation of the tissues in a solution of formaldehyde seemed to give the lymph nodes a

quality of firmness which considerably facilitated their dissection, for earlier dissection of the tissues in the fresh unfixed specimen was very unsatisfactory.

It was felt that some question might arise as to whether the extremely small bits of tissue described as lymph nodes might not be simply small collections of fat in the mesentery. Furthermore, the adequacy of the dissection with regard to stripping the node free from adherent tissues might be questioned, as even a small amount of tissue left clinging to such a small object would affect its weight value tremendously. Therefore, nodes of variable size were picked at random during

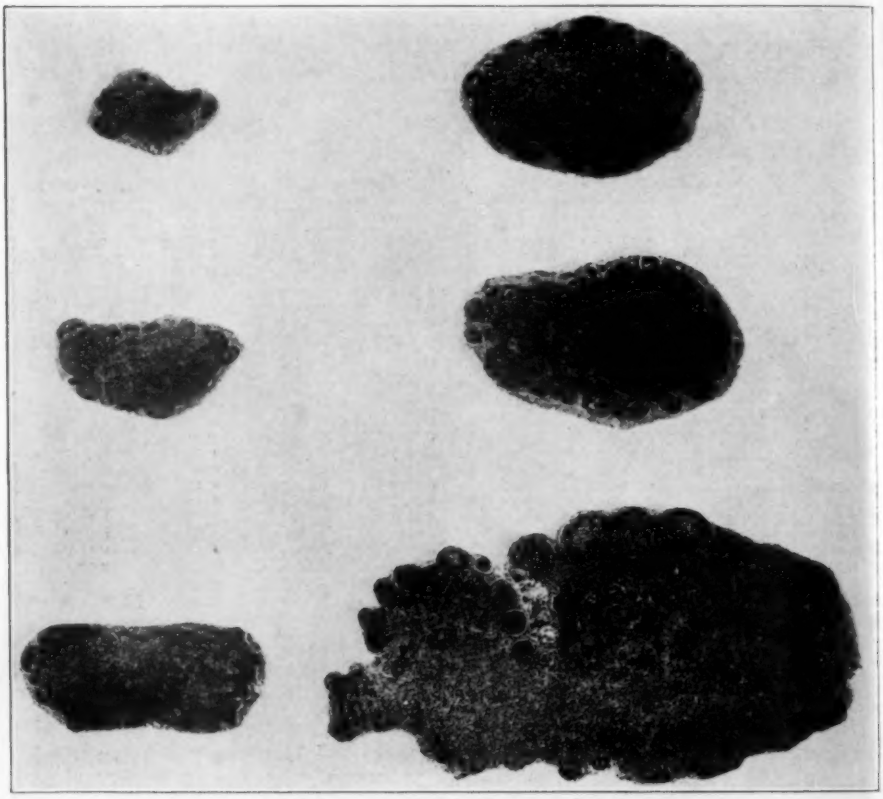

Fig. 5.—Photomicrographs of a series of mesenteric lymph nodes to show that the small bits of dissected material are lymphoid structures and to show how little adherent extraneous tissue is present following careful dissection. The nodes vary in weight from 0.0001 to 0.5 Gm; × 8.

the dissections, and after their weights had been recorded in the usual fashion, microscopic sections were made. Figure 5 shows this series of nodes, which vary in weight from 0.0001 to 0.5 Gm., and demonstrates clearly that the tissue is lymphoid and that the nodes have been dissected free down to the capsule, with practically no adherent extraneous tissue.

The mesentery was replaced in the fixative solution after the dissection of each node had been completed, and the free node was dried before being weighed. The

drying process consisted of removing any apparent excess fluid that might be present by gently rolling the node over absorbent paper.

The lymph node was then weighed on a chemical balance. A question immediately arose as to the advisability of single or multiple observations on weight. Consequently, a series of lymph nodes were weighed once and the single result recorded. Again, each node was weighed five times, and an average of each series of weight tabulations was computed. It appeared from this study that the initial weight was as accurate as an average based upon five records. Therefore, all the weights recorded in this article represent single determinations.

Each lymph node was treated in this way as an individual problem. The mesentery was first transilluminated; the lymph node was then carefully dissected

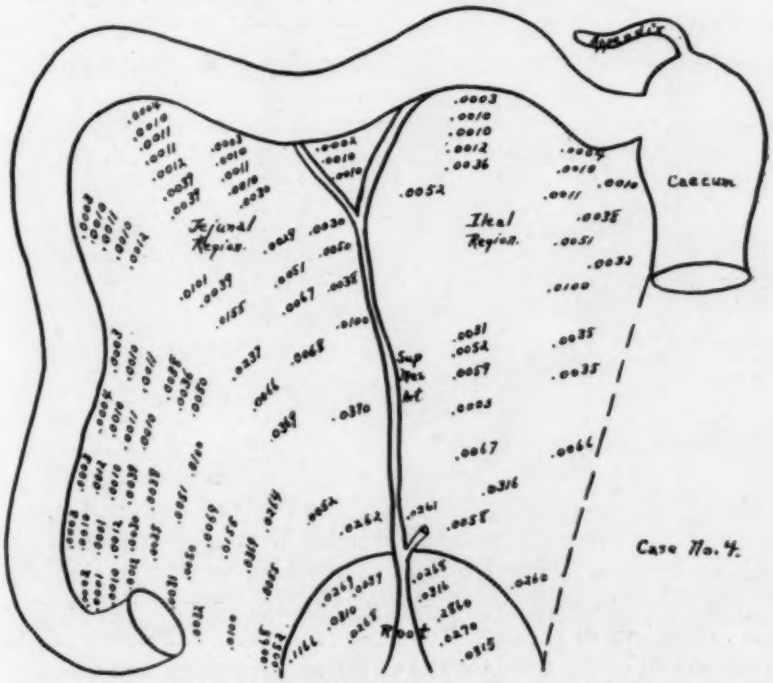

Fig. 6.—The original charts on which the weight of each lymph node was recorded in the approximate position in which it was found in the respective mesentery. The charts are organized in age sequence and labeled with the case number. The portions of the intestinal tract which were attached to the mesentery and the arbitrary regions of dissection are indicated.

free; it was dried on absorbent paper and weighed. This process was carried out on 6,008 individual lymph nodes which were encountered in the fifty specimens studied.

It was felt that each observation should be recorded as accurately as possible in order that any obscure but significant factors might not be overlooked. Consequently, an outline of the mesentery was drawn for each specimen, and the determinations of weight were recorded on the sketch in as near the same position as each node was found in the specimen. Figure 6 illustrates this method of recording the original observations.[1]

1. Reproduction of the recorded observations on the other forty-nine specimens has been omitted because of lack of space.

Observations.—Transillumination of the mesenteries of several specimens before commencing dissections indicated an apparent graduation of size of the nodes in various regions. The nodes along the intestinal margin of the mesentery, for instance, appeared to be the smallest, and those at the root of the mesentery appeared to be the largest. Therefore, an area arbitrarily marked off as the root region was indicated on the record chart of each specimen. Furthermore, examination of the record charts after a few dissections had been completed revealed a slight suggestion of greater weight of the nodes in the region of the ileum and ileocecal junction than in the region of the duodenojejunal junction and jejunum. The central branch of the superior mesenteric artery, as it coursed through the mesentery, was indicated in each chart as an arbitrary division line between the jejunal and the ileal regions.

Inspection of the reproduction of the charts (fig. 6) on which the original observations were recorded shows clearly how most of the smallest lymph nodes were consistently present in the periphery or intestinal margin of the mesentery. However, a comparison of the average weights of lymph nodes of the jejunal and ileal regions (table 2) fails to confirm the impression that nodes are larger in the ileal region. This observation seems to be of significance in view of the descriptions of the mesenteric lymph nodes by older writers in which it was repeatedly stated that the largest lymph nodes are encountered along the largest blood vessels, most of which are in the ileal region. The latter region contains the largest branches of the superior mesenteric artery, and yet the average weight of the lymph nodes in that region does not seem to vary significantly from the average weight of the nodes in the jejunal region. It is clear from table 2, however, that the average weight of the lymph nodes of the root region far exceeds that of those of both the jejunal and the ileal regions.

The weights of the respective nodes were mentally gaged during the course of the dissections. Thus, an attempt was made to guess with fair accuracy whether one node was larger than another. Furthermore, the nodes were inspected for possible correlation between the apparent size of the nodes and the actual size, as determined by their respective weights. It was observed during the entire course of the dissections that there was a close correlation between the actual weight of a node and the visual impression of its size. Thus, a small node generally weighed less than a large node, and there was apparently little deviation in the density of the tissue involved which might make a small compact node as heavy as a large loosely woven node. In other words, the apparent size of the node was indicative of its weight.

This observation seemed to be of some importance from a clinical point of view, for if a surgeon has a fairly accurate concept of the normal size of lymph nodes in the mesentery, his recognition and evaluation of the size of nodes in pathologic conditions of the mesentery should be of definite significance. Thus, it would seem safe to decide that descriptions of enlargement of the mesenteric nodes by surgeons familiar with the usual appearance of the mesentery are in all probability correct. In order to test this observation further six cases were chosen at random after the dissections had been completed. The dissected nodes in each case were then examined, and 4 nodes were chosen; a very small one, a large one and 2 of intermediate size. They were

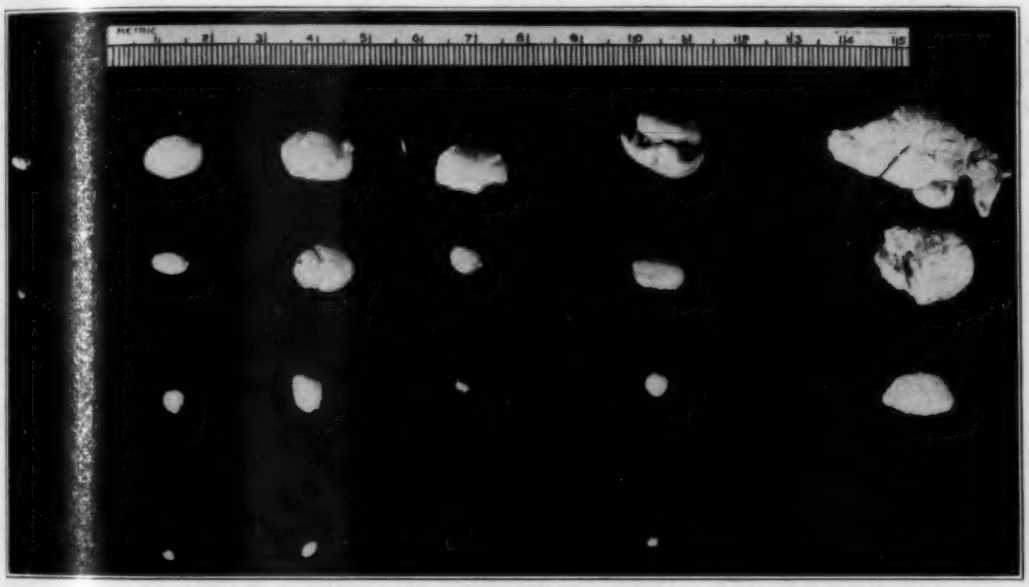

Fig. 7.—Nodes chosen by inspection, in which there is an apparent variation in size. The smallest nodes actually weigh the least and the largest nodes weigh the most.

then weighed to determine whether or not there was a correlation between their observed size and their actual weight. In each instance the apparently smallest node weighed the least, and the actual weight of each node became greater with an increase in the gross size (fig. 7). This test would seem to lend credence to descriptions of enlarged mesenteric nodes by clinical observers.

TREATMENT OF DATA

Data derived from individual examination of 6,008 mesenteric lymph nodes were first recorded on the fifty case charts. The material was

then organized as shown in table 2 according to age, sex, cause of death, number of lymph nodes and weight of the tissue, in order to facilitate a more panoramic study, which might suggest certain conclusions.

The cases were listed in age sequence from birth to 12 years according to the total number of lymph nodes, the total weight and the average weight of the lymph nodes. Furthermore, the number of lymph nodes and the average weight of the nodes for the jejunal, ileal and root regions were recorded.

Inspection of the tabulation shows a marked preponderance of new-born infants. The reasons for this imbalance of specimens according to age have already been given. There was considerable variation in the number of lymph nodes, and it is interesting to note that both the smallest and the largest number of nodes were encountered in the group of new-born infants. The number of nodes varied from 26 in a 7 month premature infant to 289 in a full-term stillborn infant.

The total amount of lymphoid tissue present in each mesentery varied from 0.0298 Gm. in a 6 month premature infant to 18.654 Gm. in an 8 year old child. The average weight of the lymph nodes for each mesentery varied from 0.0002 Gm. in a 7 month premature infant to 0.2095 Gm. in a 6 year old child. The smallest node encountered in the dissections weighed 0.0001 Gm. and the largest weighed 1.78 Gm. There was an apparent steady increase in the total weight of the lymphoid tissue of the mesenteries from birth to 12 years of age. The average weight of the lymph nodes followed this general trend closely. Furthermore, the average weight of the nodes of the arbitrarily designated jejunal, ileal and root regions seemed to follow the same trend.

Graphic analysis of the data was then carried out in order to verify or negate those impressions (fig. 8). The average weights of the lymph nodes in the specified regions and the average weight of the nodes for each complete mesentery were plotted against the age in years. The jejunal and ileal regions in each case, as well as the average weight of the lymph nodes derived from the total lymphoid tissue in the mesentery are represented in centigrams. It was necessary to plot the average weights of the root region in decigrams because of the larger numerical values encountered.

Each graph emphasizes the larger number of cases in the group of the new-born and the rapidly diminishing number with increase in age. There is a definite verification of the impression, gained from an inspection of table 2, that the average weight of the mesenteric lymph nodes increases with age. Graphic analysis of the various arbitrarily demarcated regions of the mesentery indicates that all follow the same trend.

A marked deviation from the steady increase in weight with age is noted between the ages of 8 and 12 years. The significance of this is conjectural, as only one case of a 12 year old subject was available. Consequently, the variance from the general trend might well be due to an inadequate number of cases. The fact that the weight of the nodes at the mesenteric root in this case continued to become greater somewhat substantiates this possibility. Further comment, such as argumentation favoring a peak of growth at about 12 years of age with gradual recession of the lymphoid tissue, is not necessary because of the minimal amount of available material studied during this age period.

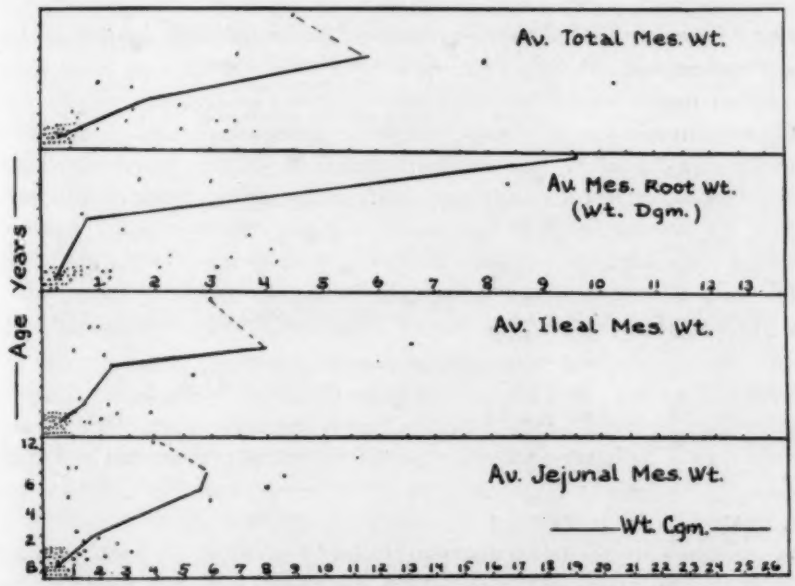

Fig. 8.—A graphic analysis of the average weights of the lymph nodes of the mesentery and its arbitrarily demarcated regions. The weights for the mesentery as a whole and for the ileal and jejunal regions are recorded in centigrams. Those for the root region are recorded in decigrams, because of the large numerical values encountered. The ages are recorded in years. The dotted portions of the curves indicate the deviation from the steadily ascending line to the single case in a 12 year old child.

Examination of the tabulated figures for the jejunal, ileal and root regions reveals an apparent increase in the average weight of their nodes. For example, the smallest average weight of nodes in the jejunal region was found to be 0.0001 Gm. in a 7 month premature infant; the largest was 0.0904 Gm. in an 8 year old child. The smallest and largest average weights in the ileum of the same cases varied from 0.0002 Gm. to 0.1297 Gm., respectively. The smallest average weight

in the root region was encountered in the same 7 month premature infant, 0.0011 Gm., and the largest was found to be 0.9564 Gm. in a 12 year old child.

The manifest difference in the average weight of the lymph nodes of the arbitrary regions of the mesentery with a progression from jejunum to ileum to root suggested a statistical analysis of available data.[1] The mean of the number of lymph nodes and the mean of the average weights of the nodes for the three regions were established. The standard deviation and the standard error of the means were calculated. Comparisons were made as recorded in table 4. A significant difference between the number of nodes in the jejunal and ileal, the

TABLE 4.—*Comparison of Means for Number of Nodes and Their Average Weights in the Jejunal, Ileal and Root Regions*

Regions		Difference of Mean	Standard Error of Difference	Ratio	Probability
		Number of Nodes			
Jejunum (Mj ± S.E.) 63.56 ± 2.72	Ileum (Mi ± S.E.) 39.82 ± 3.7942	23.74	4.66	5.094	0.000,000,6
Jejunum (Mj ± S.E.) 63.56 ± 2.72	Root (Mr ± S.E.) 16.78 ± 8.3714	46.78	8.802	5.314	0.000,000,04
Ileum (Mi ± S.E.) 39.82 ± 3.7942	Root (Mr ± S.E.) 16.78 ± 8.3714	23.04	9.190	2.507	0.012
		Average Weights			
Jejunum (Mj ± S.E.) 0.0122 ± 0.0029	Ileum (Mi ± S.E.) 0.0127 ± 0.0028	—0.0005	0.00403	—0.125	0
Jejunum (Mj ± S.E.) 0.0122 ± 0.0029	Root (Mr ± S.E.) 0.0962 ± 0.0258	—0.0840	0.0259	—3.2432	0.0014
Ileum (Mi ± S.E.) 0.0127 ± 0.0028	Root (Mr ± S.E.) 0.0962 ± 0.0258	—0.0835	0.0259	—3.223	0.0014

jejunal and root and the ileal and root regions is demonstrated by these comparisons. There is, however, no real difference between the average weight of the nodes in the jejunal and ileal regions. Comparisons of the average weights of the lymph nodes of the jejunal and root and the ileal and root regions show a decided difference.

1. These calculations were made in the following manner:

$$\text{Mean} = \sqrt{1x} = \frac{\Sigma x}{n}$$

$$\sqrt{2x} = \frac{\Sigma x^2}{n}$$

$$n2x = \sqrt{2x} = (\sqrt{1x})^2$$

$$\text{Standard deviation of the mean} = \sigma x = \sqrt{n2x}$$

$$\text{Standard error of the mean} = \text{S.E.}_m = \frac{\sigma x}{\sqrt{n-1}}$$

COMMENT

The clinical aspects of mesenteric lymphadenitis have been dealt with in considerable detail. Many points of similarity between the tuberculous and nontuberculous types have been pointed out. Possibilities for confusion of the two entities have been shown to be present, especially in the early manifestations of the disease process. Their individuality, however, depends more on the fact that the etiologic agents are different than on divergent symptomatology. Thus, the reaction of the human organism to tuberculous and pyogenic invasion of the mesenteric lymph nodes is much the same. Yet the impression is gained that the tuberculous type progresses steadily to calcification, or the end-stage of tuberculous infection, while the pyogenic type is transient and self-limited. The two types of etiologic agents in all probability gain access to the mesenteric lymph nodes in the same fashion, the reaction of the body and the local nodes being essentially the same as in infections in other locations. It is generally accepted that the cervical and inguinal lymph nodes may be enlarged following either tuberculous or nontuberculous infections of the regions drained by them. There is every reason to expect that the mesenteric lymph nodes react to infection of the regions drained by them in much the same fashion. It is therefore concluded that tuberculous and nontuberculous mesenteric lymphadenitis are separate clinical entities.

The treatment of enlargement of the mesenteric nodes has been surgical or supportive. No mention has been noted, in the considerable surgical literature relative to tuberculous mesenteric lymphadenitis, regarding the use of roentgen therapy. Yet the treatment is well known and accepted in tuberculosis of the cervical and inguinal lymph nodes, for it was one of the first conditions to be treated successfully with roentgen rays. The earliest reports regarding the use of roentgen rays in the treatment of cervical tuberculous adenitis were made in this country in 1903 by Williams, Varney and others, and in recent years the literature on the subject has become voluminous. Good articles, many of which contain excellent illustrations and careful technical descriptions, have been published by Weil, Boggs and others. MacKee stated that while there are no available comparative statistics, it is the prevailing opinion that irradiation together with general medical treatment is more successful in a majority of cases of severe local tuberculous cervical adenitis than is surgery, in point of clinical cure, permanent cure, discomfort and disfigurement. Radium has not yet been employed extensively in the treatment of tuberculous adenitis. The literature contains few reports of such treatment. Molyneux reported the successful treatment of thirty patients with radium without radium sequelae. Therapeutic results are considered to be the same with both agents. Roentgen ray treatment of tuberculous adenitis has been used with

brilliant results in Germany and has been applied by roentgenologists to tuberculous mesenteric lymphadenitis (Müller). The treatment of this condition has been successful, and has been recommended (Birk and Schall). The technic is essentially the same as for treatment of tuberculous peritonitis.

It is clear that this study has embraced only a small segment of a great problem, in which one portion at a time must be completed before a comprehensive picture may be formed. The original hope of establishing a definite concept of the normal size of the mesenteric lymph nodes has been only partially realized. The incomplete solution of the problem has been due to the many uncontrollable factors affecting such an investigation, the most important of which has been the lack of suitable material. The impossibility of obtaining absolutely normal specimens has been pointed out. Yet it would seem that even this complicating factor does not completely disqualify conclusions that may be drawn. This reaction is based on the obvious fact that all other studies of such a nature have been affected by similar uncontrollable factors, and that consequently this study may justly be correlated with them.

Analysis of the data collected by the status lymphaticus investigation committee (Young and Turnbull) supports this contention. The report discussed the size of lymphoid structures, such as the faucial tonsil, cervical lymph glands, mesenteric lymph glands and Peyers' patches in children ranging in age from birth to 16 years. The causes of death are segregated into a so-called normal group, which includes accidents, burns, hemorrhage, poisoning, epilepsy, foreign bodies, drowning and the like, and an abnormal group comprising pneumonia, gastro-enteritis, intussusception, volvulus, intestinal obstruction, appendicitis, meningitis, peritonitis, septicemia, congenital heart disease and the like. The report concluded that comparison of the normal with the abnormal values shows no evidence that the amount of lymphoid tissue is influenced in a special manner by diseases of the type described. Hellman and White and Hammar noted in various illnesses and general infections that the lymph nodes remain essentially unchanged, and that local conditions do not affect the entire lymphoid structure. They expressed the belief that the reaction of the lymphoid tissues to infection is late, and that it proceeds parallel to the formation of antibodies.

Such evidence, indicating that the common acute and subacute pathologic processes occurring in children do not affect the size of the nodes, is presented merely to show that similar investigations are not free from this complicating factor.

The investigation has been somewhat curtailed owing to the scarcity of material between 8 and 15 years of age. Nevertheless it is evident from an inspection of table 2 and figure 16 that there is a fairly steady increase in the average mesenteric weight of the lymph nodes with

advancing age and development of the body. The graphic illustration (fig. 16) of the steady rise in weight of the lymph nodes associated with an increase in age partially confirms the lymphoid type of growth curve recorded by Scammon, for there is a rapid rise in infancy and childhood and a more gradual rise toward puberty. The remaining portion of the growth curve has not been completed, for the study has not as yet been extended beyond the age of adolescence.

The effect of malnutrition or inanition on the weight of the nodes must be considered in a study of this nature. It should be remembered that inanition in these cases is usually secondary to an acute or subacute infectious process which has finally caused death. Some idea of its effects may be gained from studies regarding changes in the weight of the thymus gland during health and disease, for in early life this organ is extremely active in the reticulo-endothelial system. Boyd showed conclusively that there is a distinct loss of weight in this organ when illness has lasted more than twenty-four hours. According to Jackson, lymphoid structures such as the mesenteric nodes undergo atrophy with inanition. It is usually agreed that the condition follows closely on illness in children, and consequently one would expect the nodes in all cases with acute or subacute disease processes to be somewhat atrophic. Jackson, however, pointed out that infection involving the local nodes usually causes them to become engorged and swollen. Prolonged illness without involvement of the local mesenteric nodes and infectious processes definitely affecting them are recorded in table 2 as causes of death. The purpose of this discussion is not to evaluate the effects of the disease processes on the mesenteric nodes, but simply to point them out as uncontrollable factors affecting the study.

The study does not intend to stress the topography of the mesentery and its lymph nodes. Yet incidental knowledge has been obtained which includes verification of data regarding the location of lymph nodes in the mesentery. The older writers (Mascagni and Cruikshank) described the variation in the number of nodes and the fact that the smaller nodes seemed to be in the periphery of the mesentery while the larger ones adhered to the major blood vessels. Those observations are corroborated in this study. Additional information has been gained, however, for the root region has been established as the location of the largest mesenteric nodes.

The conclusions of earlier investigators that there is an increase in the size of the nodes with advancing age through adolescence have been confirmed. Furthermore, the impression that under certain conditions the mesenteric lymph nodes are probably enlarged has been partially substantiated, for it has been demonstrated that more confidence may now be placed in clinical observations. In other words, it has been shown that visual impressions relative to the size of nodes are fairly accurate.

I hope that the data recorded herein may be of value in further similar studies, although the initial aim of the investigation has not been completely fulfilled. The broad field for further similar investigation is manifest.

SUMMARY AND CONCLUSIONS

1. A detailed review of tuberculous and nontuberculous mesenteric lymphadenitis shows that the two entities are closely allied and suggests that they may be slightly divergent manifestations of a fundamental disease process.

2. It is concluded that tuberculous and nontuberculous mesenteric lymphadenitis are separate clinical entities.

3. The use of roentgen ray therapy for tuberculous mesenteric lymphadenitis is suggested.

4. No absolutely normal mesenteric lymph nodes are available for study, except those of stillborn infants.

5. Lymphoid tissue placed in formaldehyde, U.S.P. (1 : 10), returns to its prefixed weight after two months.

6. Lymph nodes weighing as little as 0.0001 Gm. can be dissected free from the mesentery without the adherence of other tissues.

7. The smallest lymph nodes are located near the intestinal margin of the mesentery; the largest are in the mesenteric root.

8. There is a fairly steady increase in the average weight of the nodes from birth to 12 years of age.

9. There is a significant difference between the number of nodes in the jejunal, ileal and root regions of the mesentery.

10. There is no significant difference between the average weights of the nodes of the jejunum and ileum. There is a real difference between the average weights of the nodes of the jejunal and ileal regions and the root region.

11. Visual differentiation is accurate, for the apparent size of a node is fairly indicative of its weight.

12. The effects of infection and inanition cannot be evaluated accurately in a study of this nature. They do not condemn the conclusions just mentioned, for they are present in all similar data.

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CLINICAL USE OF A PLASTIC PYLOROJEJUNOSTOMY IN CHRONIC DUODENAL ULCER

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The satisfactory results of surgical treatment of such a variable pathologic lesion as chronic peptic ulcer should be increased by the selection of the safest and most satisfactory operation for each condition.

The introduction of a plastic pylorojejunostomy with excision of the ulcer, when it is indicated, offers considerably less risk than a gastric resection. It will also permit side-tracking the ulcer with a more normal gastric physiology and less danger of jejunal ulcer than by closing the pylorus and performing a gastrojejunostomy.

A number of factors have a bearing on the choice of surgical treatment of peptic ulcer.

In the etiology of ulcer, infection has been considered of both primary and secondary importance. While acute ulcers may be produced experimentally by infection, it is likely that similar lesions arising clinically promptly heal in the absence of a spasmophilic tendency or ulcer diathesis (Alvarez [1]).

Ivy and Fauley [2] failed to produce chronic ulcer by direct infection of the gastric antrum. They explained the genesis of ulcer in man by emotional disturbances which, through pylorospasm, disturb the emptying of the stomach and may mechanically rupture a blood vessel in the mucosa. Gastric retention causes augmented motility and prolongs the contact of a highly acid gastric juice which has been shown to lower the resistance of the mucosa. The corrosive action of the acid gastric juice has been demonstrated by Mann and his associates [3] to be the most potent factor in the genesis of chronic ulcer by its almost constant occurrence after gastrojejunostomy when the duodenal contents are diverted to the ileum.

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1. Alvarez, W. C.: The Causes of Peptic Ulcer, Am. J. Surg. **18**:207, 1932.

2. Ivy, A. C., and Fauley, G. B.: The Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, Am. J. Surg. **11**:531, 1931.

3. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923. de Takáts, G., and Mann, F. C.: Ann. Surg. **85**:698, 1927.

Ivy and Fauley demonstrated that a number of additional factors are also present. They sutured the end of the stomach to the end of the jejunum, with diversion of duodenal juices to the ileum, and ulcers occurred in all experiments, but after suturing to the side of the jejunum, ulcers occurred in only 45 per cent. When the duodenal juices were drained into the antrum after an end-to-end gastrojejunostomy, ulcers occurred in only 16 per cent of experiments, but when later diverted to the ileum, ulcers appeared in 87 per cent. After suture of the end of the stomach to the side of the duodenum, with diversion of alkaline juices, ulcer occurred in only 10 per cent of the subjects of the experiment. After section of the duodenum 1 inch (2.5 cm.) below the pylorus and suture to the jejunum, with diversion of the duodenal contents, ulcers developed below the suture line in 66 per cent of the subjects. The method of anastomosis would seem to be more important than the susceptibility of the mucosa to ulcer.

The results of the experiments suggest that a jejunal ulcer would be less than one half so likely to occur after a properly performed end-to-side pylorojejunostomy as after a gastrojejunostomy.

Longitudinal anastomosis of the jejunum to the pylorus with the proximal loop attached to the incision in the antrum might result in better regurgitation than anastomosis at right angles. If the duodenal secretions prove to be diverted into the stomach as well after a pylorojejunostomy as after section of the jejunum and reimplantation into the antrum (a somewhat more complicated technic) the incidence of jejunal ulcer should be reduced to about one-tenth that after a gastrojejunostomy.

The short loop of jejunum may be sutured in position above the transverse mesocolon after anastomosis to the pylorus, if desirable. It is possible that a slight jejunal stasis below the stoma may aid in the prevention of a recurrent ulcer, although I have seen duodenal stasis associated with duodenal ulcer.

Contributing factors to ulcer have been proved to be: a small stoma or stenosis of the pylorus; roughage in the diet which delays emptying and traumatizes tissue; the motor drive; trauma at operation; failure of normal neutralization by duodenal juices, and a gradual increase of susceptibility of the mucosa to the acid juices from above downward in the intestine.

Pyloric stenosis alone has been shown experimentally not to give rise to gastric ulcer, but may delay its healing. Isolated pouches of the whole stomach have resulted in peptic ulcers near the fistula, but none along the lesser curvature (Moutier [4]).

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4. Quoted by Alvarez.[1]

Morton [5] showed the presence of a mechanical factor by reducing the force of ejection of acid chyme from the stomach, with fewer ulcers.

Keppich [4] permitted the duodenal secretions to flow high up into the fundus in a few experiments with a low end-to-side gastrojejunostomy, and found fewer jejunal ulcers after removing the distal end of the stomach. Koennecke [4] isolated the pars pylorica with the first part of the duodenum and anastomosed them to the ileum and found no ulcers, refuting the aforementioned implication that the secretions of the antrum and duodenum might predispose to ulcer.

Other factors than the acid gastric juice must predispose to ulcer, since under normal conditions acute lesions of the stomach heal readily. In addition, various organs and parts of the intestine have been transplanted into the stomach wall without being digested, as long as the circulation was intact (Ivy and Fauley). Although transplants of jejunal mucosa into the anterior wall of the stomach and antrum have not resulted in ulcers (Ivy and Fauley), Mann obtained them on transplantation into the lesser curvature.

Goldberg [6] and Harper [7] found that a peptic ulcer always developed in the small intestine where it was sutured to a Pavlov or acid-secreting pouch of the stomach.

However, Harper showed that when a secreting pouch of the antrum was anastomosed to the intestine free acid was not present and no ulcer formed. He was able to prevent ulcers adjacent to Pavlov pouches by coating the mucosa with an emulsion of gelatin, acacia, olive oil and lecithin twice a day.

Alvarez stated that certain foods, including the peptones, exerted a protective action on the cells of the mucosa during digestion.

The importance of peristalsis was shown by Bollman and Mann,[8] who found no leak from a gastric fistula into the intestine and no ulcer if peristalsis was directed toward the stomach.

Pathologically, a chronic peptic ulcer shows sclerosis of the blood vessels, which increases with the chronicity of the condition (Wellbrock [9]). The vascular fibrosis, with the indurated connective tissue bed, must be important factors in the failure to heal under favorable

5. Morton, C. B.: Observations on Peptic Ulcer: A Method of Producing Chronic Gastric Ulcer, Ann. Surg. **85**:207, 1927.

6. Goldberg, S. S.: A Method of Producing Peptic Ulcer Experimentally, Ann. Surg. **96**:155, 1932.

7. Harper, F. R.: Experimental Peptic Ulcer, Proc. Staff Meet., Mayo Clin. **7**:318 (June 1) 1932.

8. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

9. Wellbrock, W. L. A.: Duodenitis and Duodenal Ulcer, Ann. Surg. **91**:533 (April) 1930.

medical or surgical treatment. The frequent occurrence of large arteries in the base of the ulcer explains the severe hemorrhages.

In the healing of chronic peptic ulcer there are four fundamental objectives: first, rest to the ulcer; second, improvement of the local blood supply; third, removal of the cause, and, fourth, restoration of normal gastric function.

Various medical treatments, including attempts to neutralize the acid secretions, have resulted in a large percentage of failures.

Brown [10] reported from a follow-up of one thousand, two hundred and twenty-four patients that 49 per cent were cured and 16.5 per cent improved by the Sippy treatment, which included rest under hospital management. He believed that the poor results in about 20 per cent of the patients were due to extensive fibrosis of the ulcer from lack of early medical treatment, and that this group should have received surgical treatment.

Alvarez stated that no medical treatment neutralizes the acid secreted during the night.

Pylorospasm has been considered as one of the important factors to control in the treatment of ulcer, since it produces retention with high acidity and may prevent normal regurgitation of the duodenal contents.

Alvarez reported that experimentally the neutralizing power of the duodenal secretions is greater than that of the pancreatic secretions and the latter is better than that of bile.

The stomach may be divided into two main portions by the incisura angularis: the fundus, and the antrum, or pyloric part. Experimental work has shown that the fundus is less actively motile and acts as a reservoir, while the muscular antrum is chiefly concerned with mixing and expelling the food. The mechanism controlling the pyloric sphincter is obscure, but it responds to the acidity of the stomach and duodenal contents as well as to the type and consistency of food (Howell [11]).

Bayliss [12] has shown that normally the amount of regurgitation of duodenal juices increases with the acidity of the gastric contents.

The secretion of the antrum is always alkaline (Howell). The mucosa contains no acid-secreting cell, but only a mucoid type of cell (Bensley [13]).

Edkins [14] stated that products of digestion in contact with the antrum stimulate gastric secretion by an action of the hormones. However,

10. Brown, Ralph C.: Results of Medical Treatment of Peptic Ulcer, J. A. M. A. **95**:1144 (Oct. 18) 1930.

11. Howell, W. H.: Textbook of Physiology, ed. 10, Philadelphia, W. B. Saunders Company, 1927.

12. Bayliss, W. M.: Principles of General Physiology, New York, Longmans, Green & Co., 1924.

13. Bensley, quoted by Howell.[11]

14. Edkins, quoted by Bayliss.[12]

it has been shown by Priestley and Mann [15] that there is no change in the gastric acidity in Pavlov pouches after either exclusion or excision of the pyloric part of the stomach.

In the surgical treatment of peptic ulcer Balfour [16] stated that all requirements for a good result are satisfied by removal of the lesion and by establishment of an adequate means of emptying the stomach.

Bevan [17] observed that, in general, the best surgical treatment for duodenal ulcer was a gastrojejunostomy and for gastric ulcer, a resection of the stomach.

In small ulcers, Balfour advocated either a pyloroplasty or a gastrojejunostomy, with local excision when possible. In lesions of the posterior wall of the duodenum he advised excision of the ulcer with a cautery or a knife, followed by a pyloroplasty. Judd and Hazeltine [18] stated that such operations can be done in 50 per cent of patients with duodenal ulcer with slightly better results and with a lower mortality than a gastro-enterostomy.

Gastroduodenostomy and pyloroplasty with or without excision of the ulcer have not been used widely because of the frequency of adhesions, the large number of ulcers of the posterior wall and the necessity for a more exacting technic. There is also a rather frequent recurrence of the ulcer and a persistence of symptoms (Bevan; Meyer and Rosi; [19] Horsley; [20] Hurst [20]). Pyloroplasty in ulcers of the posterior wall would not seem indicated, since either the ulcer is left or excision of it leaves a new wound which may leak or fail to heal.

Walton [21] stated that neutralization of the acid secretions did not take place at a high enough level after gastroduodenostomy to be satisfactory in ulcers of the lesser curvature.

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15. Priestley, J. T., and Mann, F. C.: Gastric Acidity with Special Reference to the Pars Pylorica and Pyloric Mucosa: Experimental Study, Arch. Surg. **25**:395 (Aug.) 1932.

16. Balfour, D. C.: (*a*) Management of Lesions of the Posterior Wall of the Duodenum, Surg., Gynec. & Obst. **49**:806 (Dec.) 1929; (*b*) Gastric Ulcer and Its Treatment, in Collected Papers of Mayo Clinic, Philadelphia, W. B. Saunders Company, 1931, vol. 23, p. 70; (*c*) The Advisability of Early Operation for Duodenal Ulcer, West. J. Surg. **40**:28, 1932; (*d*) Results of Gastro-Enterostomy for Ulcer of the Duodenum and Stomach, Ann. Surg. **92**:558, 1930; (*e*) Causes of Unsatisfactory Results in the Surgical Treatment of Peptic Ulcer, Collected Papers of Mayo Clinic, Philadelphia, W. B. Saunders Company, 1930, vol. 22, p. 56.

17. Bevan, Arthur D.: S. Clin. North America **12**:18 (Feb.) 1932.

18. Judd, E. S., and Hazeltine, M. E.: The Results of Operation for Excision of Ulcer of the Duodenum, Ann. Surg. **92**:563 (Oct.) 1930.

19. Meyer, K. A., and Rosi, P. A.: Successive Perforation of Two Anastomotic Marginal Ulcers in the Same Patient, S. Clin. North America **13**:1251 (Oct.) 1933.

20. Quoted by Meyer and Rosi.[19]

21. Walton, A. J., in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1928, vol. 5, chap. 2, p. 43.

Fortunately, the percentage of cures after a gastrojejunostomy when the ulcer has been left to heal, has been very high. Balfour [16b] reported 89 per cent of satisfactory results in gastric ulcers and Gatewood,[22] 82 per cent, including all peptic ulcers. Gaither,[23] in a personal follow-up, found 80 per cent of complete cures after gastrojejunostomy, and 72 per cent of cures after various conservative operations, with 19 per cent improved and only 9 per cent unimproved. He stated that in view of the low mortality as compared to subtotal resection, there was no justification for displacing the conservative types of operation. Alvarez stated that in duodenal ulcer gastrojejunostomy is the best operation, as from 80 to 90 per cent of the patients are relieved.

Jejunal ulcer occurs with varying frequency, but its incidence is probably about 3 per cent after gastrojejunostomy (Bevan; Balfour; Alvarez; Benedict [24]). However, it may be very high when there is a stenosis or exclusion of the pylorus. Schwarz [4] reported stenosis in eighty-three of one hundred and thirty cases of gastrojejunal ulcer. Eiselsberg [4] found ulcers of the jejunum in over 25 per cent of cases in which exclusion of the pylorus had been done with a gastrojejunostomy.

Exclusion above the antrum is sometimes done (Devine; [25] Alvarez). The contention is that by leaving the antrum, duodenal peristalsis is strengthened, and better neutralization is obtained at the gastrojejunostomy stoma. However, there may be a weaker stimulation of the alkaline secretions by food emptying only into the jejunum and actually less efficient duodenal expulsion of the juices, since jejunal ulcers still occur and even the duodenal ulcer does not always heal.

Jejunal ulcer is more likely to follow any method of gastrojejunostomy which prevents easy access of duodenal secretions about the stoma (Mann) and also inadequate neutralization or mixing in the stomach.

The gastrojejunostomy stoma, Walton believed, should be at the greater curvature. If made higher, it will not empty readily unless the patient is lying down. He believed that if the stoma is placed near the pylorus, especially if the ulcer is near it, the antrum will greatly assist evacuation.

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22. Gatewood: Immediate Mortality and Late Results of Operations for Peptic Ulcer Performed in Presbyterian Hospital, Chicago, Between 1915 and 1930, Ann. Surg. **92**:554 (Oct.) 1930.

23. Gaither, E. H.: Eventual Results of Gastric Surgery, J. A. M. A. **101**:966 (Sept. 23) 1933.

24. Benedict, E. B.: Jejunal Ulcer, Surg., Gynec. & Obst. **56**:807 (April) 1933.

25. Devine, H. B.: Basic Principles and Supreme Difficulties in Gastric Surgery, Surg., Gynec. & Obst. **40**:1 (Jan.) 1925.

Experimentally, Cannon and Murphy [26] found food passing entirely through the pylorus after gastrojejunostomy, but clinically the stomach empties through both the pylorus and the stoma. The amount passing either is probably dependent on their relative size, the amount of spasm (Walton) and the location of the stoma.

The healing of a duodenal ulcer after a gastrojejunostomy may be dependent on the improved contact with alkaline juices, together with lessened acidity in the stomach and more rapid emptying. The frequency of return of a healed duodenal ulcer following the taking down of a gastrojejunostomy for jejunal ulcer is well known.

Lahey [27] reported the reactivation of a duodenal ulcer after a subtotal resection of the stomach with the ulcer excluded, before removal at a second-stage operation. He stated that any satisfactory surgical treatment must offset the effects of pylorospasm either by a direct operation on the sphincter or by a gastro-enterostomy.

Following gastrojejunostomy, undetermined factors sometimes delay evacuation and prolong the secretion of acid. I [28] have observed this experimentally in animals with a Pavlov pouch and also clinically.

The incidence of gastrojejunal ulcer following gastric resection is believed by Strauss and his co-workers [29] to be between 1 and 2 per cent. St. John [30] reported it after 3.6 per cent of gastric resections and Gatewood after 10 per cent.

Lahey stated that the mortality of primary gastric resection is too high, even if as low as 6.7 per cent. He found the mortality was 20 per cent after resections for jejunal ulcer. Postoperative jejunal paralysis or local peritonitis may cause acute gastroduodenal dilatation after jejunal resections. If unrelieved by a duodenal tube, reoperation with short-circuiting or jejunostomy may save the patient's life.

In large ulcers Balfour advised a partial duodenectomy with gastric resection, if too much does not have to be removed. He reported resection in 75 per cent of chronic gastric ulcers in 1931. Emerson and Czirer [31] reported resection of all callous ulcers of the stomach.

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26. Cannon, W. B., and Murphy, F. T.: Movements of the Stomach and Intestines in Some Surgical Conditions, Ann. Surg. **43**:512, 1906.

27. Lahey, F. H.: The Selection of the Operative Procedure for Various Gastric and Duodenal Lesions, S. Clin. North America **13**:541 (June) 1933.

28. McWhorter, G. L.: Some Clinical and Experimental Observations on Gastric Acidity, Am. J. M. Sc. **155**:672, 1918.

29. Strauss, A. A.; Bloch, L., and Friedman, J. G.: Gastrojejunal Ulcer, J. A. M. A. **90**:181 (Jan. 21) 1928. Strauss, A. A.; Bloch, L.; Friedman, J. G.; Meyer, J., and Parker: Subtotal Gastrectomy for Duodenal Ulcer, ibid. **95**:1883 (Oct. 18) 1930. Strauss, A. A., in discussion on Gaither, E. H.: Gastric Surgery, ibid. **101**:966 (Sept. 23) 1933.

30. St. John, F. B.: Ann. Surg. **92**:597, 1930.

31. Emerson, E. C., and Czirer, L.: Surg., Gynec. & Obst. **56**:927 (May) 1933.

The surgical treatment for peptic ulcer by resection of the anterior half of the pyloric sphincter was reported by Deaver and Burden [32] in a series of cases to give as good results as either gastrojejunostomy or resection of the stomach.

A wedge resection of the fundus of the stomach has been advocated by Connell [33] for chronic ulcer. This operation removes a large part of the acid-secreting mucosa, but does not interfere with the pyloric mechanism.

Roholm [34] abandoned circular resections of the stomach because of frequent recurrent ulcers in the scar.

The choice of any one of a number of conservative operations demands further knowledge of the disturbed physiologic relations and the benefits to be expected by different operations on the type of ulcer present.

Recognition of the extent of pathologic changes is necessary to determine the importance of excision of the ulcer and the most conservative operation which should give relief.

The persistence of old ulcers due to fibrosis after good medical management or a conservative operation probably explains the lack of relief in many patients. Since many callous ulcers are on the posterior wall of the duodenum, either excision or exclusion by a conservative operation may be obtained by a pylorojejunostomy.

The method of plastic pylorojejunostomy described here permits excision of the ulcer without resection of the stomach. If excision of the ulcer is not advisable, the duodenum may be closed above the ulcer, which can be resected later if desirable.

There are both technical and physiologic advantages of pylorojejunostomy over the Billroth I and II technics or their modifications (Bevan), a gastrojejunostomy, a partial gastric exclusion, or a gastric resection. The motor mechanism of the stomach and antrum is maintained for normal mixing and emptying. The alkaline juices of the antrum are retained. The dangerous ulcers of the lesser curvature after resection are avoided. Mechanical drainage of the stomach may be improved by swinging the antrum down and to the left through the transverse mesocolon.

Theoretical objections are supported by inconclusive physiologic experiments. Resection of the antrum, which has been thought to lessen the stimulating action of the hormones and relieve the muscular

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32. Deaver, J. B., and Burden, V. G.: Ann. Surg. **92**:533 (Oct.) 1930.

33. Connell, F. G.: Resection of the Fundus of the Stomach for Peptic Ulcer, Ann. Surg. **96**:209, 1932.

34. Roholm, K.: Value of Circular Resection in Chronic Gastric or Duodenal Ulcer, Ugesk. f. læger **95**:573 (May 18) 1933; abstr., J. A. M. A. **101**:332 (July 22) 1933.

motor drive, has given no better results than a gastrojejunostomy (Roholm). Crohn [35] reported that there was achylia in all cases he had followed up in which subtotal gastrectomy had been done. Neither small nor wide resections of the stomach have fulfilled expectations in the treatment of ulcer. A recurrent ulcer occurs frequently, even after the Billroth I operation (Bevan).

Unless achylia is obtained by radical resection the preservation of the antrum should aid neutralization. Pylorojejunostomy permits this with conservation of normal physiologic relations, although it seems evident that the pyloric sphincter should be cut well into the antrum, permitting a wide anastomosis to the jejunum.

Jejunal ulcers would seem to be more frequent when the anastomosis is made to the acid-bearing part of the stomach than to the antrum, although there are several factors involved, such as the size and location of the stoma, the emptying time, the motor drive and the intragastric and extragastric mixing of the alkaline and acid juices.

Andrews [36] has recently supported the growing evidence that there is a tendency to the formation of a jejunal ulcer by the pouring out of unneutralized acid juice when the stoma is placed high up in the acid-secreting part of the stomach.

The small number of serious complications following conservative surgical procedures in patients not completely relieved with good medical management is assurance that if the proper operation is performed fewer failures will result.

A competent medical authority (Brown [10]) has stated that patients with callous ulcers should be treated surgically. Conservative operations will relieve the majority. When excision of the ulcer seems indicated and a pyloroplasty is impossible or the lesion is on the posterior wall of the duodenum, a pylorojejunostomy is far safer than gastric resection. It may also be used in a patient whose condition is otherwise inoperable or who is a bad risk. The chances of a jejunal ulcer may be minimized by proper technic and medical management. Reoperation should be easier than after gastric resection.

The radical gastric resection should be reserved for patients with extensive lesions shown to be resistant to conservative operations. Until knowledge or adequate tests have been acquired to determine which complications occurring after conservative operations will not occur after radical ones, one should choose the former. Conservative surgical intervention for types of ulcer shown to resist medical treatment is consistent with the routine medical treatment for all uncomplicated cases of early peptic ulcer.

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35. Crohn, B. B., in discussion on Eggleston, E. L.: Pathologic Conditions Secondary to Achlorhydria, J. A. M. A. **97**:1216 (Oct. 24) 1931.

36. Andrews, E.: Jejunal Ulcer, S. Clin. North America **13**:1251 (Oct.) 1933.

REPORT OF A CASE

Diagnosis.—The following case was one of chronic perforating duodenal ulcer into the pancreas.

History.—J. W., a German man, aged 53, was examined on Feb. 19, 1933. The present complaint was "stomach trouble" for fifteen years, consisting of severe epigastric distress and frequent vomiting. He was rarely free from pain for more than two or three weeks at a time, but it was worse in the fall and winter.

The distress and pain usually came on within three or four hours after eating. This had become worse during the preceding few months, and during the month prior to examination the pain had been almost constant. Certain foods, such as fat meat, cabbage, sauerkraut, condiments, salt, pepper, tomatoes, apples, bananas and tea, gave more distress. Until the previous month he had been able to take a light diet of milk, farina or oatmeal, eggs, celery, spinach, well cooked vegetables, cake and pie, except apple pie. During the previous month he ate practically nothing, and was afraid to take even milk. He had some relief by drinking hot water and vomiting during the preceding two years. Soda gave relief for a few minutes.

When he was working as a laborer, up to a few years previously, he ate rapidly.

Examination at a clinic five years before, revealed heart trouble and roentgen evidence of an ulcer of the duodenum. He had been treated for the cardiac condition ever since. For several years he had some dyspnea on exertion. He worked only seven months during the preceding five years and none during the last two and one-half years, owing to the cardiac and gastric complaints.

Chronic bronchitis had been present for about twenty-five years, with a rather dry cough.

He smoked about forty cigarets a day for fifteen years, often waking and smoking during the night. He never drank alcohol. He had had no previous illness except a few bad colds. He lost his teeth in an accident twenty years before and had used plates ever since.

His average weight was about 158 pounds (71.7 Kg.) up to five years before examination. He lost gradually from that time until at examination he weighed 110 pounds (49.9 Kg.). Some days during the previous year he lost 3 or 4 pounds (1.3 to 1.4 Kg.), and then regained it slowly.

Sugar was found in the urine about eight months before. He had been under treatment for this and for the ulcer since then.

Three months before examination he was treated for his ulcer for six weeks in a large hospital. He was in bed for four weeks on the Sippy diet. He was never free from pain except when his stomach was pumped. Heat and hot milk gave some relief from the severe pain. For the previous month, since leaving the hospital, although still on a diet and alkalis, the gastric symptoms had become worse, so that he was afraid to eat anything and had become very weak.

Physical Examination.—The patient was well developed, but considerably emaciated. False teeth were used. The lungs showed no definite changes.

An examination of the heart was made at the cardiac clinic on March 10. The pulse rate was 120 and the blood pressure 90 systolic and 80 diastolic. There was a presystolic and systolic murmur, indicative of aortic stenosis and regurgitation. An electrocardiogram showed a P R interval of 0.2 and a Q R S interval of 0.06. There was a slurring of the R wave in all three leads, with a notching in lead II. The T and P waves were normal in amplitude, but the voltage in all three leads was low. The consultant stated that myocardial damage had occurred, and that the patient was not a good operative risk.

There was considerable tenderness on abdominal palpation over the region of the duodenum, with some muscle spasm.

Roentgen examination showed a deformity of the first part of the duodenum characteristic of an ulcer perforating into the pancreas (fig. 1). There was increased gastric peristalsis. No six hour retention was present.

The urine before operation contained granular casts, occasional white blood cells and many bacteria, but no albumin or sugar.

Examination of the blood on April 12 showed: hemoglobin content, 81 per cent; red cells, 4,000,000; white cells, 7,000; polymorphonuclears, 60 per cent; small lymphocytes, 30 per cent, and large lymphocytes, 10 per cent. The Wassermann and Kahn tests were negative.

At this time the patient's heart had been thoroughly digitalized, and the cardiac rate was 60. There was no definite improvement in the gastric symptoms, and operation was decided on.

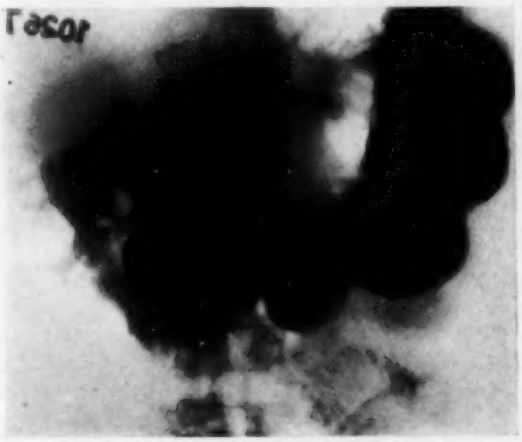

Fig. 1.—Roentgenogram taken before operation, showing a typical large perforating ulcer of the posterior wall of the duodenum.

Operation.—A plastic pylorojejunostomy was performed on April 19, with resection of a chronic perforating ulcer of the posterior wall of the duodenum into the pancreas. Regional local anesthesia with 0.5 per cent procaine hydrochloride was used.

A right paramedial incision was made. The stomach was normal, but the pylorus was considerably dilated. There was a large palpable mass involving the first part of the duodenum and the pancreas. There was some stippling on the lower side of the first part of the duodenum. The duodenum was incised just below the pylorus, and a huge ulcer crater was seen extending over the dilated posterior wall. The bed of the ulcer was formed by hard, dense, fibrous scar tissue on the pancreas, and measured 4.5 by 5 cm. in diameter. The active ulcer rim of the crater, which extended slightly forward on the anterior wall, was about 0.5 cm. wide and high.

The duodenum was cut across completely just below the pylorus and the ulcer rim excised, leaving as much of the anterior duodenal wall as possible. Only the active ulcer margin was removed (fig. 2), leaving the dense, boardlike fibrous base on the pancreas. There was little bleeding. The lower end of the duodenum

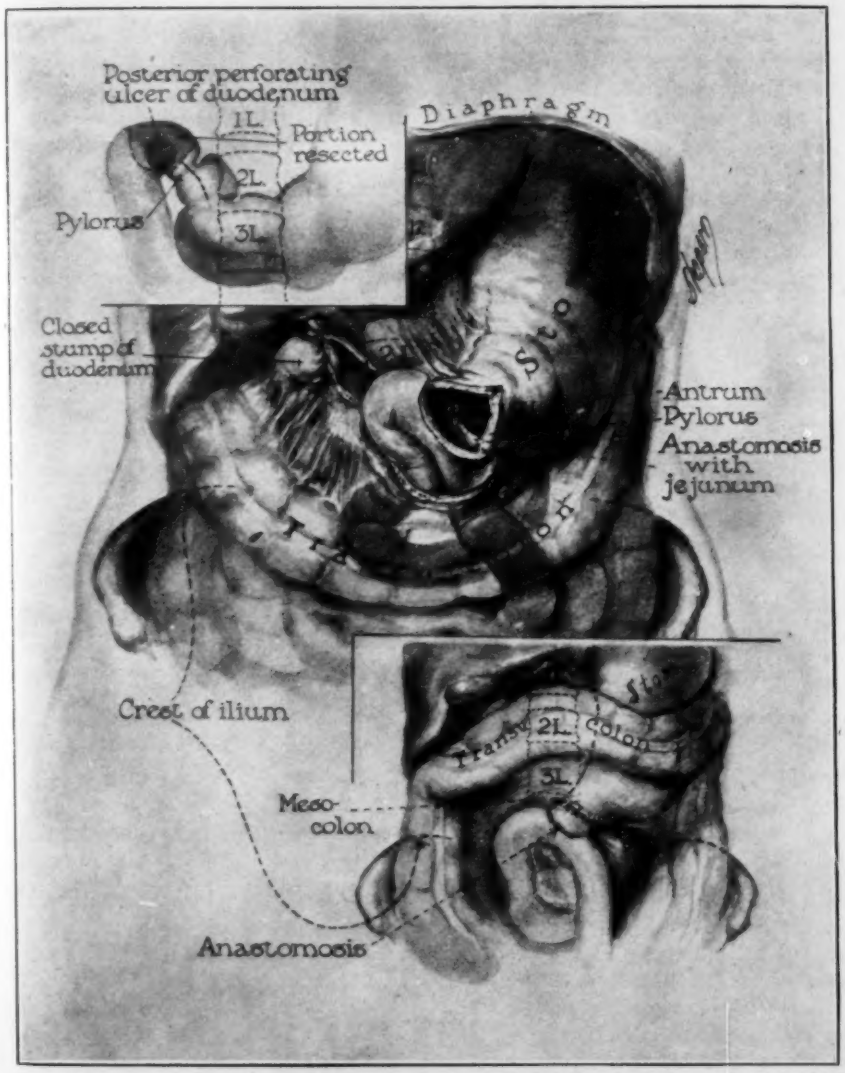

Fig. 2.—Technic of plastic pylorojejunostomy. The ulcer was excised and the stump of the duodenum invaginated. The lower end of the stomach was anastomosed to the jejunum and then fixed beneath the mesentery of the transverse colon. In the upper and lower insets the position of the stomach was copied from roentgenograms taken before and after operation.

was invaginated with fine silk sutures without using a clamp, following my technic reported elsewhere.[37]

The pyloric end of the stomach was freed for a short distance from the mesentery of the liver, the pancreas and the transverse colon, without injury to the blood supply. An opening was made in the transverse mesocolon similar to that for a gastrojejunostomy, and a loop of jejunum about 8 inches (20.3 cm.) from the ligament of Treitz was brought through it. A longitudinal cut was made through the anterior wall of the pylorus, extending about 1 inch (2.5 cm.) into the antrum of the stomach. A few blood vessels in the cut edges were ligated. The loop of jejunum was placed with the distal part downward against the enlarged pyloric end of the stomach and an anastomosis made, using three rows of chromic catgut sutures (fig. 3). The loop of jejunum with the attached pyloric end of the stomach was then pushed down through the hole in the mesentery. The edges were sutured to the antrum just above the line of anastomosis. A small collapsible drain was placed near the base of the ulcer on the pancreas, which was covered with omentum, and the abdomen closed.

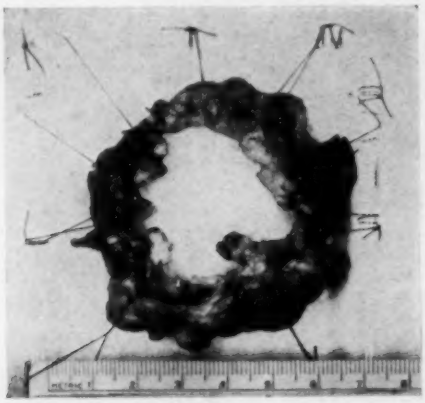

Fig. 3.—Excised perforating ulcer of the duodenum. The indurated fibrosed base was not removed.

Microscopic sections of the edge of the ulcer showed round cell infiltration, with only dense fibrous tissue at its base.

Postoperative Course.—There were no complications. The drain was removed on the second day.

The patient was given a bland diet, with no alkalis. Complete relief from the previous gastric distress was obtained.

Three months later there was a gain of 20 pounds with a general gain in strength. Eight months after operation there was a further gain of 23 pounds, to a weight of 153 pounds (69 Kg.).

Roentgenograms three and six months after operation showed the pyloric end of the stomach considerably lower and to the left of its former position (figs. 2, 4 and 5). There was excellent peristalsis with rapid emptying. One hour and fifteen minutes after a barium sulphate meal the stomach was almost empty. Four hours after the meal the barium was all in the ascending colon.

37. McWhorter, G. L.: An Original Method of Closure of a Partially Aperitoneal or Short Intestinal End, Surg., Gynec. & Obst. **50**:1037 (June) 1930.

Fig. 4.—Appearance six months after operation. The pyloric end of the stomach was lower and more to the left than before the operation.

Fig. 5.—The stomach was practically empty one and a fourth hours after a barium meal.

An Ewald meal was given, and showed a free hydrochloric acidity of 49 and a total acidity of 72. No blood was present.

Examination of the urine on Oct. 15, 1933, revealed considerable sugar, but otherwise gave negative results. A blood sugar test showed 272 mg. He was given a diabetic diet. His general condition was good. He was moderately active and able to do a little work, but his heart pounded on exertion. On examination twenty-two months after operation he was still on a diabetic diet and was working as a watchman. The urine was sugar-free and there were no complaints of gastric disturbance.

CONCLUSIONS

1. A conservative surgical procedure, when the general condition is satisfactory, is indicated in the treatment of many callous ulcers. Complications may require a radical operation and necessitate greater risk.

2. The surgical procedure should be adjusted to relieve the disturbed physiologic relations as well as the pathologic changes.

3. A plastic pylorojejunostomy has been used clinically with success when excision of an extensive callous duodenal ulcer perforating into the pancreas seemed imperative in a patient who was a poor risk.

4. Wider indications, including exclusion of a duodenal ulcer, may be found for pylorojejunostomy, which offers a better physiologic restoration than the most widely used operations and a lower mortality than gastric resection.

STAPHYLOCOCCIC EMPYEMA AND PYOPNEUMOTHORAX

PATHOGENESIS, PATHOLOGY, SYMPTOMS AND TREATMENT

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The occurrence and varying incidence of the staphylococcus in infections of the lung and of the pleura have been commented on by a number of observers, but the significance of pulmonopleural lesions due to the staphylococcus appears to have been overlooked. The literature consists essentially of statistical presentation of the incidence of the staphylococcus in pleuropulmonary infections, although staphylococcic pneumonia has been the subject of some separate discussion. Despite the fact that higher mortality has been noted, staphylococcic pleural infections have been included with the other bacteriologic varieties as if their pathogenesis, symptoms and treatment presented no appreciable differences. We believe that there are distinctive features in the pathogenesis and pathologic changes and in the treatment of staphylococcic pulmonopleural suppuration. The lesion in the form of empyema or pyopneumothorax will be described as an entity, and we shall attempt to show that its consideration as such leads to more clearly defined therapeutic measures.

INCIDENCE

The available literature can be surveyed briefly, for it is chiefly concerned with incidence. As early as 1892 Netter [1] noted the staphylococcus in pure culture in 8 per cent of cases in a postmortem study of bronchopneumonia. Holt and Howland [2] in 1913, found the organism in 8 per cent of cases of empyema in children. In a study conducted at Mount Sinai Hospital in 1915 Wilensky [3] reported the incidence of staphylococcic empyema as 10 per cent. Chickering and Park [4] described

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From the surgical service of Dr. Harold Neuhof and the laboratories of Mount Sinai Hospital.

1. Netter, P.: Étude bactériologique de la bronchopneumonie, Arch. de méd. expér. et d'anat. path. **4**:28, 1892.
2. Holt, L. E., and Howland, J.: The Diseases of Infancy and Childhood, ed. 9, New York, D. Appleton & Company, 1926, p. 442.
3. Wilensky, A. O.: Empyema of Thorax, Surg., Gynec. & Obst. **2**:501, 1915.
4. Chickering, H. T., and Park, J. H.: Staphylococcus Aureus Pneumonia, J. A. M. A. **72**:617 (March 1) 1919.

a large number of cases of staphylococcic pneumonia occurring during an epidemic of influenza. The incidence of the staphylococcus as the cause of pneumonia is much lower under ordinary circumstances, as pointed out by Cole.[5] Nevertheless the staphylococcus is a common cause of empyema, the incidence given being as high as 22 per cent in one report (Heuer[6]).

The frequency and significance of staphylococcic empyema in infants will be referred to shortly. In a study of empyema in children below the age of 2 years, Rienhoff and Davison[7] found the staphylococcus in 19.5 per cent. Hart[8] reported an incidence of 17.5 per cent in a series of cases of empyema in children. Various authors have noted the incidence of staphylococcus in postmortem studies of bronchopneumonia in children: Lyon[9] reported 9.6 per cent, and Menter, Bailey and DeBone[10] reported 8 per cent. Reports of these and other investigators show that the staphylococcus is not a rare cause of pneumonia in children and is a common cause of empyema. If distinguishing features of pleural infections due to the staphylococcus have been noted they have not been described in any of the papers we have seen.

Because we observed the extraordinary frequency of staphylococcic empyema in very young infants in our service at Mount Sinai Hospital we examined the bacteriologic reports on all the cases of empyema from 1928 to 1932. There were 373 patients, of whom about half were children (182) and half adults (191). The incidence of the staphylococcus in adults was 5.7 per cent (11 cases) and in children under 13 years of age 17 per cent (31 cases). Much more striking, however, was the fact that 15 of the 21 cases of empyema in infants under 1 year of age were due to the staphylococcus (71 per cent). An additional significant fact is that half of all the cases of staphylococcic empyema in children in our series occurred in the first year of life.

PATHOGENESIS

Although this article deals with staphylococcic pleural infection, the causative pulmonary lesion obviously requires first consideration.

5. Cole, R. I.: Acute Pulmonary Infections, De Lamar Lectures, 1927-1928, Baltimore, Johns Hopkins University, School of Hygiene and Public Health, 1929.

6. Heuer, G.: Acute Empyema, J. Thoracic Surg. **1**:461 (June) 1932; in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1927, vol. 4, p. 503.

7. Rienhoff, W. F., and Davison, W. C.: Empyema in Infants Under Two Years of Age, Arch. Surg. **17**:676 (Oct.) 1928.

8. Hart, D.: Empyema in Children, South. M. J. **9**:823, 1930.

9. Lyon, A. B.: Bacteriologic Studies of One Hundred and Sixty-Five Cases of Pneumonia and Postpneumonic Empyema in Infants and Children, Am. J. Dis. Child. **23**:72 (Jan.) 1922.

10. Menter, M. L.; Bailey, S. F., and DeBone, F. M.: Pneumonia in Children, J. Infect. Dis. **51**:254 (Sept.) 1932.

The two most likely sources of the focus or foci in the lungs are the bronchial tree and the blood stream (the question of lymphatic origin will not be discussed). The information at hand at the present time is inconclusive as to which of these pathways commonly conducts the infection to the lungs, for the difficulties of interpretation are obvious. A staphylococcic abscess of the kidney or of a bone is generally recognized as a metastatic focus, but proof is often lacking. For identical reasons a staphylococcic abscess of the lung can properly be placed in the same category unless evidence exists to prove its origin by aspiration. It may be argued that Staphylococcus aureus is to be found in the nasal secretions of normal adults (30 per cent, Neumann) and that the organism can be isolated frequently from the throat of a normal person as well as from sputum obtained from the bronchi. Aspiration may account for staphylococcic pneumonia, which does not appear to differ appreciably from pneumonia due to other organisms, but it does not explain as readily an isolated abscess or multiple abscesses due to the staphylococcus. On the other hand, the evidence of an embolic (metastatic) origin of the staphylococcic abscess of the lung is sometimes clear. Leaving aside the characteristic miliary abscesses of the lungs occurring during sepsis caused by the staphylococcus, there are not a few instances in which solitary or multiple abscesses of the lung occur in persons who are known to have had staphylococcic bacteremia. A distant source of surface infection, such as paronychia, is the sole evidence in other cases, as in staphylococcic abscess of a kidney or of a bone. In a third group, simultaneous metastatic abscesses in other parts of the body as well as in the lung comprise the evidence for staphylococcic abscess of the lung as a metastatic focus Finally, the appearance of the pulmonary suppurative lesion at autopsy is quite unlike that of aspiration bronchopneumonia with secondary suppuration.

The embolic origin of many cases of staphylococcic abscess of the lung is stressed for practical rather than for theoretical reasons. The purpose is twofold: first, to indicate that the prognosis is potentially graver in any case of staphylococcic empyema than in a case of the more common pneumococcic empyema because the underlying infection in the lung may be embolic and therefore one of a number of metastatic foci, and, second, to indicate that an appreciation of metastatic origin leads to the conception of an abscess of the lung and not of staphylococcic pneumonia as the pathologic process underlying the empyema. The clinical significance of this view will be shown.

In our series of cases definite portals of entry for general staphylococcic invasion were noted in 22.5 per cent of the children and in 45.5 per cent of the adults. The sites were chiefly active or subsiding skin infections (from a number of which Staph. aureus was isolated in pure culture). The histories in this group were often strongly suggestive

of metastatic pulmonopleural lesions rather than of the typical sequence of pneumonia and empyema. In the remaining cases, however, there was little if anything in the history or clinical course to differentiate the staphylococcic from the common pneumococcic infection in the lung and empyema.

In the cases in young infants in our series a history clearly indicative of the metastatic origin of the staphylococcic infection was common. There were 2 striking examples of sepsis of birth, and it is of interest to note that both patients recovered. In 1 infant there were multiple periarticular abscesses at the age of 2 weeks followed shortly thereafter by pyopneumothorax. Dunham's [11] study on sepsis in the new-born confirms our impression that the majority of, if not all, cases of staphylococcic empyema in young infants (which means the great majority of all cases of empyema in young infants, as we have stated) are derived from embolic abscesses of the lungs.

PATHOLOGIC PROCESS

In generalized staphylococcic sepsis, empyema secondary to miliary abscesses of the lung is an occasional complication. It rarely requires clinical consideration under such circumstances and is not under discussion in this paper.

The pathologic process in the underlying lung determines the character and the extent of the pleural lesion in staphylococcic empyema. The pulmonary lesions may be single or multiple. The solitary abscess (or group of abscesses) is comparable to the staphylococcic carbuncle of the kidney or the osteomyelitic abscess of the bone. The lesion can properly be termed a "carbuncle of the lung" by analogy to carbuncle of the kidney. The similarity of carbuncle of the kidney, with its cortical involvement, perinephritis and perinephritic abscess, to subpleural carbuncle of the lung, with contiguous sacculated empyema or pyopneumothorax, is evident. In our series all the patients presented suppurative pleuritis at the site of the carbuncle of the lung. Of the 11 adult patients, 5 had sacculated pyopneumothorax at the time of operation, and in 3 bronchial fistulas appeared subsequently as evidence of the rupture of a pulmonary suppurative focus. Of the 31 children, 12 had pyopneumothorax at the time of operation, and bronchial fistulas appeared at a later date in 8 others. Approximately the same percentage in each group gave evidence of the rupture of a pulmonary suppurative focus as the source of the empyema or pyopneumothorax. The data at hand therefore point to an identical process in adults and children. As will be pointed out, however, the clinical manifestations of pleural invasion in children are often different from those in adults.

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11. Dunham, E. C.: Septicemia in the New-Born, Am. J. Dis. Child. **45**:228 (Feb.) 1933.

The pulmonary involvement may not be limited to a solitary abscess or a group of abscesses or to a carbuncle in one lobe. Abscesses may be scattered in more than one lobe or even in both lungs. Occasionally the degree of involvement in children may be so great that a lobe is largely destroyed by the suppurative process. Recurrent pyopneumothorax as the result of successive ruptures of multiple abscesses in the lung occurred in several patients in our series. It is obvious that the mortality in some instances of staphylococcic empyema or pyopneumothorax can be ascribed to the extent and degree of invasion of the lung and not to the pleural infection. This was true in all the cases in our series that came to postmortem examination.

The pathologic process in the pleura depends on the site of the pulmonary focus, its extent and the rate of destruction of the overlying parenchyma. In adults the pleural involvement is usually slow and benign. The empyema or pyopneumothorax develops gradually in encapsulated form. Bronchial communications, when present, are generally insignificant, indicating that the abscess in the lung was probably small and subpleural. Our experience with staphylococcic empyema or pyopneumothorax of adults has been limited, but the architecture has been characteristic in the few cases we have encountered. The collection of pus is in two pockets, with a shelf of infiltrated lung bearing the perforated or nonperforated parenchymal focus lying between them. The encapsulations are dissimilar in size, and the shelf may narrow greatly the communication between them. The surgical significance of this configuration is evident. In our first experience at operation in 1 of these cases the second and larger collection of pus was entirely overlooked after the first had been evacuated and was accidentally revealed beyond a shelf of lung as a result of coughing.

The slow evolution of empyema or pyopneumothorax which has been described as the adult form is also encountered in children. It is not typical of childhood, however, and is less and less frequently seen as the earliest years of life are approached. The characteristic lesion in childhood, and more particularly in infancy, is wide rupture of a staphylococcic abscess of the lung into the pleural cavity. When it evolves slowly, permitting walling-off adhesions to form, pyopneumothorax with little or no displacement of the mediastinum is the result. On the other hand, total pyopneumothorax with great shift of and tension on the mediastinum occurs when the abscess develops rapidly with early rupture. Never present in adults in our series, this picture occurred in one third of the children and in almost all the infants.

CLINICAL ASPECTS

The symptoms of staphylococcic pleural infections obviously depend on the pathologic process. Although there may be some overlapping,

four classes of cases can be indicated as follows: (1) sacculated empyema; (2) sacculated pyopneumothorax; (3) total or subtotal empyema with or without mediastinal tension, and (4) total or subtotal pyopneumothorax with or without mediastinal tension.

The first two forms, which we have termed the adult type, can be dismissed at once, for there is nothing in the symptoms to distinguish them from other varieties of empyema. The history comprises the only basis on which the lesions can be suspected to be staphylococcic. As already stated, the history was suggestive of pulmonary metastasis in 45.5 per cent of the adult cases.

The third and fourth varieties, which we have termed the childhood type, present symptoms that range from mild to severe depending on the speed of the accumulation of pus with or without air in the pleural space. The severest cases are those in which the early rupture of the focus in the lung leads to air being blown into the infected pleura with a one way valve action. The shift of the mediastinum is rapidly progressive, with correspondingly increasing tension on the mediastinal structures and embarrassment of the heart and of the opposite lung. The clinical picture is dramatic. The patient is a young child, or more often an infant, who has been ill only a few days. Suddenly there develop severe dyspnea, cyanosis, tachycardia and high fever. Within a few hours the child is in collapse, and death may ensue quickly with the manifestations of asphyxia. When death does not supervene the child remains cyanotic, dyspneic and toxic. Only rarely does gradual compensation for the abrupt shift of the mediastinum occur. There may be an interval of partial relief, followed by a recurrence of the extreme manifestations. On examination the evidences of shift of the heart and of the trachea are found, together with the physical signs of air and fluid in the chest. If mechanical relief is not given, a progressive displacement of the mediastinum will be noted. In other cases empyema or pyopneumothorax has been present for several days with little or no mediastinal tension, and the symptoms have been mild and insignificant. Suddenly the alarming symptoms supervene, and the child presents an urgent problem for relief. Other forms of pulmonary abscesses rupturing into the pleura may present identical clinical pictures, but the occurrence in the early years of life, and particularly in infancy, is distinctive of the staphylococcic lesion. If, in addition, there is a history or clinical course which suggests that the pulmonopleural lesion is metastatic and, of course, if there are other metastatic foci, there should be no doubt as to the staphylococcic origin of the pleural infection.

Among the children in our series were 3 patients who recovered despite the evolution of other metastatic foci. On the other hand, a child who presented no focus other than the pleural one at the time of operation had metastatic lesions subsequently and died with the

picture of sepsis. It may be impossible to evaluate the relative importance of a staphylococcic pleural infection in a child. However, the most important point we wish to make is that, on the basis of our experiences, the lesion should not be considered irremediable unless it is obviously an incidental feature in generalized staphylococcic sepsis.

ROENTGENOLOGIC ASPECTS

In Adults.—The usual finding has been that of a sacculated collection of fluid or of air and fluid without distortion of the mediastinum. Five of the 11 patients presented well defined collections of fluid. The sacculation may be lateral, mediastinal, supra-apical or infrapulmonary, depending on the site of the staphylococcic lesion in the lung. A small pyopneumothorax may simulate an abscess of the lung with a large collection of fluid and air. In our experience most sacculated large parietal collections of fluid and air are in the pleura. Accurate roentgenologic localization is essential for correct and efficient drainage. From what has been said it is clear that the roentgenographic picture of staphylococci empyema or of pyopneumothorax in adults is not distinctive.

In Children.—The roentgenographic picture is more varied, in keeping with the differences in the pathologic processes in children that have been described. The characteristic feature seen in the roentgenograms of children is a large collection of fluid and air with considerable displacement of the trachea and the mediastinum. The same condition is of course seen in other forms of ruptured abscess of the lung but it is so rarely due to other causes in children (especially in young children and infants) that it can be termed the distinctive feature of staphylococcic pyopneumothorax in the young. A careful inspection of the films will occasionally reveal more or less circular areas of rarefaction or of increased density in the pulmonary field adjacent to the pleural shadows. They represent, respectively, drained or undrained abscesses of the lung. The shadows are pathognomonic of staphylococcic infection under such circumstances, and, when present, offer valuable information regarding the extent of the pathologic process in the lung. Their absence does not, of course indicate an insignificant lesion in the lung, for the shadow of even a large ruptured abscess can be readily obscured by pleural shadows.

When films are taken with the patient lying down, the fluid level may be completely lost and a correct interpretation of the pathologic processes in the pleura and of the changes in the mediastinum may not be possible. It is therefore imperative that all films be taken in the upright posture, even if it is necessary to support the patient. Lateral films are as important as the anteroposterior or postero-anterior views

for the accurate localization of encapsulated effusions. Postoperative films are often necessary for the purpose of checking up or for the determination of a site of retention of pus. These, too, must be taken in the upright posture. The introduction of iodized oil through a sinus in the chest is often of value in the roentgen visualization of residual pockets or of communications between the pleura and the bronchial tree.

TREATMENT

Sacculated Pyothorax or Pyopneumothorax (Adult Type).—These cases are rarely urgent. The lesion should be localized accurately by physical examination, fluoroscopy and roentgenogram, because entry into the free pleura by aspiration or at operation may convert the encapsulated abscess into total empyema. Sections of one or two ribs are excised for adequate visualization and drainage. After the cavity has been emptied by suction the space is inspected with a sterile light for recesses as well as for the site of rupture. The likelihood of biloculation, as pointed out in the description of the pathologic process, should be borne in mind, and the simple evacuation of a collection of pus should not be regarded as the end of operation until the absence of an additional pocket (or pockets) has been definitely proved. In the 11 cases in adults there was 1 death. The patient had bilateral pulmonary abscesses with multiple pleural encapsulations and died of metastatic staphylococcic abscess of the brain and meningitis. The conclusion that the adult type of staphylococcic pleural infection is a relatively benign lesion not calling for special consideration should not, however, be drawn from our small series of cases. In 2 instances it was necessary to split open the underlying abscess of the lung. Extensive excision of the ribs was required in several cases. Reoperation for additional pockets, probably overlooked at the original operation, has been necessary. We know of instances not included in this series in which chronic staphylococcic abscess of the lung and chronic pleural empyema remained after the primary operations. The operation for staphylococcic empyema or pyopneumothorax should be carefully and thoroughly carried out, with examination for an unruptured subpleural abscess of the lung and drainage of the abscess should one be present. At the end of the operation all recesses are packed with gauze (iodoform) to prevent pocketing. The packings can be left in place for several days, sometimes for a week or longer, and should be replaced only when loosened by discharges.

Total or Subtotal Empyema or Pyopneumothorax (Childhood Type).—The minor procedure of closed drainage adequately cares for the acute pathologic process in the pleura, although later revision of the wound is not infrequently required for cure. Open operation in

the presence of an acutely displaced mediastinum is, of course, not to be considered. The important point is that open operation is also contraindicated with little or no displacement of the mediastinum. The basis for this statement is the difference that exists, in our opinion, between staphylococcic and pneumococcic pleural infections. Whereas mediastinal fixation is apt to be present at a relatively early stage of pneumococcic empyema, a similar fibrinopurulent fixating exudate is not to be anticipated at that time in staphylococcic pleuritis. Furthermore, a condition that begins as staphylococcic empyema without mediastinal tension may at any time become one of pyopneumothorax with great mediastinal shift. In a number of our cases closed drainage resulted in the escape of pus with little or no air at first, to be followed later by the sudden discharge of large quantities of air when the abscess of the lung ruptured into the pleura. Severe and possibly fatal mechanical disturbance might have resulted from the rupture of such an abscess into an open wound, whereas respiratory embarrassment was minimal or lacking in the presence of closed drainage.

The arguments advanced in favor of the treatment of empyema by aspiration cannot be applied with justification, in our opinion, to staphylococcic empyema or pyopneumothorax of childhood. The degree of suction employed to evacuate the pus may open a sealed-off bronchial communication or may widen an existing fistula. If the phenomena of mediastinal tension are not present they may be induced, or if present, they may be greatly increased. To indicate that this is not merely a theoretical objection we refer to a case of staphylococcic empyema in a child not in this series (because not operated on) who went into collapse shortly after therapeutic aspiration was performed and died with the picture of respiratory distress. Disaster is courted each time that therapeutic aspiration is performed, and many aspirations would be necessary in the majority of cases in order to achieve a result. Furthermore, treatment by aspiration, whether successful or not, usually means prolonged morbidity, with its invitation to complications. This is a matter of considerable importance in sick patients, particularly in infants. Finally, unsuccessful treatment by aspiration is apt to result in multiple pleural encapsulations or a fixed collapsed lung, with a major surgical problem as the sequel.

Closed drainage is a minor surgical procedure and, as has been stated, it adequately cares for the acute phase of staphylococcic empyema or pyopneumothorax of childhood. The procedure, which can be carried out at the bedside, consists of a stab thoracotomy through a small intercostal incision. A catheter or small rectal tube is introduced a short distance within the chest and is connected with a length of rubber tubing. The end of the tube is placed under water in a glass receptacle set well below the level of the chest. The only feature of the operative

procedure to be stressed is the necessity of a snug fit at the exit of the drain from the wall of the chest. The tube itself or, better, a snug rubber cuff over the tube is securely fixed to the wall of the chest with strips of adhesive tape. Adhesive strips should also approximate the skin about the drain.

The escape of pus (or air and pus) in the underwater drainage is usually profuse for the first twelve to twenty-four hours after operation, gradually diminishing in amount in the succeeding days. With a considerable bronchial communication, however, large amounts of air may be discharged for days. We have already called attention to occasional cases of staphylococcic empyema in which only pus is discharged at first, to be followed, sometimes suddenly, by the escape of air. These are instances in which the underlying abscess of the lung ruptures into the empyema cavity after closed drainage has been established. It is our distinct impression that this accident has favorably influenced the clinical course when it has occurred under such circumstances.

The escape of air from the pleural cavity by way of a bronchial communication should not be confused with the leakage of air along the drainage tube. The latter is the most important complication after closed drainage; the dangers inherent in a sucking wound are too well known to be recapitulated. The chances of leakage along the tube are reduced by a minimal skin incision, the application of a well occluding dressing at the time of operation and meticulous attention to and observation of the drainage system after operation. The child should not be able to pull at the dressings, and alterations in position should not result in traction on the tubing. Sudden changes in the patient's condition, with particular reference to dyspnea and cyanosis, should be reported promptly and should be as promptly investigated. They may be referable to a sucking wound or to obstruction of the drainage. The former is cared for by the introduction of a larger tube with strips of gauze packed between it and the edge of the incision in the soft parts. The arrest of a steady flow of pus in the first week after operation generally means plugging of the tube, which can usually be overcome by aspiration or by angulation of the tube, for which replacement may be necessary. We wish to emphasize our observation that the complete or almost complete cessation of flow of pus in the first days after operation has always meant retention of pus within the chest and not a premature cure of the empyema.

The nursing staff should receive instruction for appropriate action in the event of one of two accidents that may occur in closed drainage. One is the escape of the end of the tube from beneath the water level. The tube should be clamped off (a clamp is kept at the bedside in all cases of closed drainage) and then reinserted into the water that is in

a receptacle situated well below the level of the chest. An additional piece of tubing can be attached by means of a glass connection. The second accident is a sucking wound following the escape of the tube from the wound in the chest. All dressings should be removed by the nurse unless a physician is immediately available, and the lips of the wound should be approximated until a tube can be reinserted. In our service, calibrated glass urinals are used as the receptacles for closed drainage. The amount of drainage is measured and recorded daily. The urinal is then emptied and a measured amount of water introduced. The tube is clamped off by the nurse before the change is made. The clamp is not removed until the end of the tubing is in place below the surface of the water. We have given some space to the nursing in cases of closed drainage because correct appreciation by the nurse of the problems involved may be vital in an emergency.

The duration of efficient closed drainage varies. In some cases the intercostsal drain becomes loose in a few days, and pus leaks along the tube. The drainage remains truly closed for an average of one week. After from seven to ten days, at which time the discharge of pus is usually slight, the mediastinum is probably more or less fixed. The tube can then safely be removed, to be replaced by a tube for open drainage. Revision of drainage by the excision of a portion of a rib is often necessary; it was done in 60 per cent of our cases.

The frequency of bronchial communication has already been pointed out. Of the 11 adults 5 had bronchial fistulas at the time of the operation and 3 presented fistulas subsequently. Of the 31 children, pyopneumothorax at the time of closed drainage existed in 12, and bronchial communication appeared subsequently in 8. An actual or potential bronchial communication must therefore be assumed to be part of the picture in most cases of staphylococcic pleural infection. Accordingly, irrigation of the pleural cavity is absolutely contraindicated in the postoperative treatment. In none of our cases has the bronchial fistula been a special problem of management. Adequate drainage has meant early expansion of the lung, with spontaneous closure of the fistula as the result. The fistulas healed in all the patients and remained closed as determined by the follow-up.

GENERAL TREATMENT

The administration of oxygen with or without the admixture of carbon dioxide may save a life during the stage of acute tension. A slow intravenous drip of a 5 per cent solution of dextrose and physiologic solution of sodium chloride is invaluable in the treatment of the circulatory collapse that is so often present in the severe cases in infancy. It was maintained for many days in

several cases in our series and was, in our opinion, the decisive factor in the recovery of the patients after adequate drainage was instituted. That adequate drainage is essential for desperately sick infants should be stressed. There is a current impression that infants in such a condition do not withstand operative procedure and therefore that the less done the better. Our experience has been that prompt and adequate drainage of the suppurative focus has given them their chance for recovery. Residual pockets after primary closed drainage must be more carefully watched for than in infants or in children who are not desperately ill and must be more promptly evacuated when found. The recovery of several children in our series can properly be ascribed to active surgical treatment combined with constant supervision by the physicians of the pediatric service. Staphylococcic empyema or pyopneumothorax should be treated only in the hospital, and the patient should receive there the constant vigilance of the nursing, pediatric and surgical staffs.

COMPLICATIONS AND MORTALITY

There was 1 death from cerebral metastasis among the 11 adults, to which reference has already been made. In another patient the blood culture was positive after drainage of the empyema, but additional metastatic foci did not appear, and the patient recovered. A metastatic abscess in a kidney developed in a third patient. Complications were much commoner in children. Of the 31 children, 10 presented other metastatic foci, chiefly lesions of the bones and joints and abscesses in the soft parts. There were 13 deaths (mortality, 42 per cent). Almost exactly half of the children were under 1 year of age, and the mortality in the group of infants was 52.5 per cent. Autopsies were performed following 6 of the 13 deaths. The summary of the protocols is the best index of the gravity of staphylococcic pleural infections in childhood: (1) suppurative pulmonary focus and empyema on the opposite side; (2) suppurative pericarditis; (3) suppurative pulmonary focus and suppurative pleuritis on the opposite side and fibrinopurulent pericarditis; (4) multiple abscesses in the opposite lung; (5) multiple perforations of abscesses of the lung and pericarditis with serous effusion, and (6) multiple perforations of abscesses of the lung and fibrinopurulent pericarditis.

The comparative mortality in children in Mount Sinai Hospital with the other varieties of pleural infection for the same years (from 1928 to 1932) as those for which the staphylococcic infections have been reported is worthy of note. The other infections comprised the pneumococcic, streptococcic and anaerobic forms. There were no deaths from pneumococcic empyema or pyopneumothorax. In the group with streptococcic involvement the mortality from empyema was 15 per cent and from pyopneumothorax 25 per cent. The mortality from anaerobic

empyema (ruptured putrid abscess of the lung) was 30 per cent. These comparative figures offer further evidence that the staphylococcic infections of the pleura should not be classified with the other pleural infections but should be considered separately because of their gravity or potential gravity. This feature should be added to those we have described as distinctive in the etiology, pathology, clinical manifestations and treatment of staphylococcic pulmonopleural infections. The mortality depends, then, on the dissemination of staphylococcic foci. There should be no appreciable mortality from staphylococcic empyema or pyopneumothorax secondary to a solitary abscess of the lung when rationally conceived therapy has been employed.

SUMMARY

Staphylococcic empyema or pyopneumothorax is a definite entity, with distinctive features in etiology, pathology, clinical manifestations, treatment and mortality.

The staphylococcus is the cause of the great majority of suppurative pleural infections in infants.

The pulmonary lesion from which the staphylococcic pleural infection is derived is usually an abscess of the lung. The invasion of the pleura is by rupture of the abscess in the majority of cases.

The evidence is often clear that a staphylococcic abscess of the lung with its complicating pleural infection is a metastatic lesion. Abscesses of the lung, with or without accompanying empyema, may be multiple and bilateral. The solitary abscess is analogous in origin and in pathologic process to carbuncle of the kidney and can be termed carbuncle of the lung.

Four clinical groups are described: sacculated empyema, sacculated pyopneumothorax, total or subtotal empyema with or without mediastinal tension and total or subtotal pyopneumothorax with or without mediastinal tension. Communications with bronchi are present in the majority of cases in each group.

The first two varieties, termed the adult type, present distinguishing pathologic features but are not distinctive clinically.

The third and fourth varieties, termed the childhood type, are characterized by severe mechanical disturbances (dyspnea, cyanosis and tachycardia) if there is tension on and shift of the mediastinum. The lesion which requires relief most urgently occurs with early rupture of the abscess of the lung in infants or in young children.

Distinctive roentgenologic features of the childhood type are described.

The treatment of the adult type, rarely urgent, is by complete opening of the empyema through a liberal incision. The underlying abscess of the lung may require drainage.

Urgent treatment is often imperative for the childhood type. Closed drainage is employed, and the reasons therefor are given. Treatment by aspiration is unjustifiable for the reasons given.

The treatment by closed drainage is given in detail.

The general principles of treatment are stated.

The complications and mortality are described.